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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/18, 31/445, 31/495, C07K 5/06, 5/08 | A1

(11) International Publication Number: **WO 98/26773**

(43) International Publication Date: 25 June 1998 (25.06.98)

(21) International Application Number: PCT/US97/21532

(22) International Filing Date: 21 November 1997 (21.11.97)

(30) Priority Data:
60/032,753 17 December 1996 (17.12.96) US

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(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF MATRIX METALLOPROTEINASE INHIBITORS FOR TREATING NEUROLOGICAL DISORDERS AND PROMOTING WOUND HEALING

(57) Abstract

Matrix metalloproteinase inhibitors are useful for preventing and treating neurological disorders and in promoting wound healing.

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USE OF MATRIX METALLOPROTEINASE INHIBITORS FOR TREATING NEUROLOGICAL DISORDERS AND PROMOTING WOUND HEALING

FIELD OF THE INVENTION

This invention provides a method for treating and preventing neurological disorders such as Alzheimer's disease, and for promoting wound healing, comprising administering a compound characterized as being a matrix metalloproteinase inhibitor.

BACKGROUND OF THE INVENTION

Amyloid plaque formation is found in a number of diseases, including Alzheimer's disease, scrapie, bovine spongiform encephalophy, Gerstmann-Straussler Syndrome, and the like. The amyloid plaques comprise proteins bound together in a fibrillous matrix. Amyloidosis is the general name given to diseases and conditions characterized by the presence of amyloid protein. A number of different types of amyloid protein are known, and all types are considered pathological, since no normally occurring amyloids are known. Accordingly, the presence of amyloid protein in a host is an indication of abnormal formation of fibrils and plaques. Amyloidosis has been clinically observed in a number of disease states, including certain mental illnesses, neurological diseases, and collagenosis. Indeed, the brains of subjects diagnosed with Alzheimer's disease have one thing in common, namely an abundance of amyloid in the form of plaques and tangles.

Alzheimer's disease is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment, and emotional stability that gradually leads to mental deterioration and ultimately death. Only two clinically approved treatments are available, one being tacrine hydrochloride (Cognex®, from the Parke-Davis Division of Warner-Lambert Company). Because Alzheimer's disease and related degenerative brain disorders

are a major medical issue for an aging population, the need for new treatments and methods for diagnosing the disorders are needed.

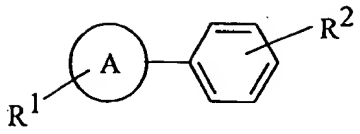
We have now discovered that compounds which inhibit the enzymes that mediate the breakdown of connective tissues are useful for treating neurological disorders and wound healing. Such enzymes are known as native matrix metalloproteinases, which are classes of naturally occurring enzymes found in most mammals. They are zinc proteases that hydrolyze collagens, proteoglycans, and glycoproteins. The classes include gelatinase A and B, stromelysin-1 and -2, fibroblast collagenase, neutrophil collagenase, matrilysin, metalloelastase, and interstitial collagenase. These enzymes are implicated with a number of diseases which result from breakdown of connective tissues, such as rheumatoid arthritis, osteoarthritis, osteoporosis, multiple sclerosis, and even tumor metastasis. To date, inhibitors of matrix metalloproteinases have not been utilized to treat or prevent neurological disorders such as Alzheimer's disease and Parkinson's disease, or to promote wound healing. An object of this invention is to provide a method for treating and preventing neurological disorders and promoting wound healing metalloproteinase inhibitor.

SUMMARY OF THE INVENTION

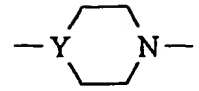
This invention provides a method of treating and preventing neurological disorders and promoting wound healing by administering an effective amount of a matrix metalloproteinase inhibitor.

The method can be practiced by administering any chemical compound that is effective in inhibiting the biological activity of a matrix metalloproteinase such as collagenase, stromelysin, gelatinase or elastase. Numerous compounds are known to be matrix metalloproteinase inhibitors, and any of such compounds can be utilized in the method of this invention.

In a preferred embodiment, the matrix metalloproteinase inhibitor to be utilized is a substituted bicyclic compound of the formula



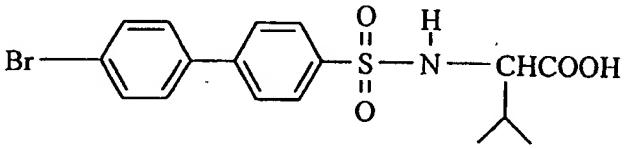
wherein:

A is phenyl or  , where Y is CH or N;

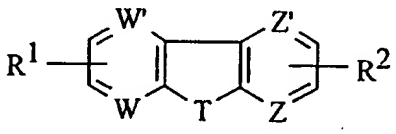
R^1 is a substituent such as alkyl, aryl, halo, amino, substituted and disubstituted amino, and alkoxy;

R^2 is carboxyalkyl ketone or oxime, or a carboxyalkyl sulfonamide such as $-SO_2NHCHCOOH$ where R^3 is alkyl, substituted alkyl, amino, substituted and disubstituted amino, and aryl.

A particularly preferred embodiment is a method of treating and preventing neurological disorders and wound healing by administering a biphenylsulfonamide such as

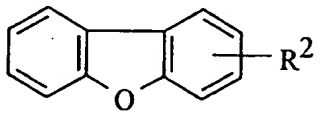


In another embodiment, neurological disorders and wound healing are treated or prevented by administering a matrix metalloproteinase which is a substituted fused tricyclic compound of the formula

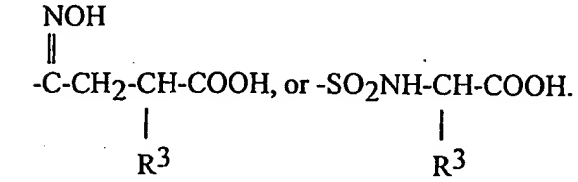


where R^1 and R^2 are as defined above, T is O, S_5 $(O)_{0,1,}$ or 2, C=O, NR^3, or $-NR^3C-$, and W, W^1, Z, and Z^1 are each the same or different and each is CR^3,

where R^3 is alkyl, halo, alkoxy, acyl, and aryl. A preferred method utilizes dibenzofurans of the above formula, for instance compounds such as



where R^2 is, for instance,



All of the matrix metalloproteinase inhibitors to be utilized in the method of this invention are either known or are readily available by common synthetic processes.

DETAILED DESCRIPTION OF THE INVENTION

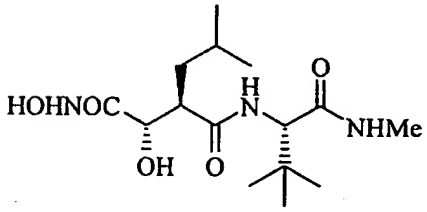
All that is required to practice this invention is to administer to a mammal suffering from a neurological disorder or suspected of developing a neurological disorder or in need of wound healing an effective amount of a matrix metalloproteinase inhibitor.

A "matrix metalloproteinase inhibitor" as used herein is any chemical compound that inhibits by at least five percent the hydrolytic activity of at least one matrix metalloproteinase enzyme that is naturally occurring in a mammal. Such compounds are also referred to as "MMP inhibitors". Numerous matrix metalloproteinase inhibitors are known, and all are useful in the method of this invention. For example, 4-biarylbutyric and 5-biarylpentanoic acid derivatives are described in WO 96/15096, which is incorporated herein by reference. The compounds are defined generally as $(T)_XA$-B-D-E-G. Over 400 specific compounds are named, and each is incorporated herein and can be employed in this invention.

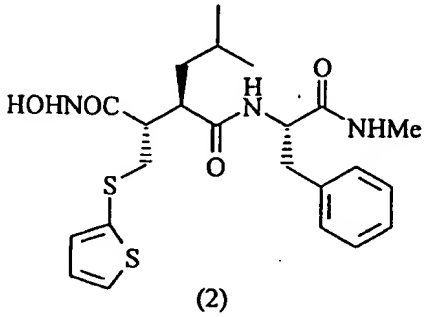
The matrix metalloproteinases (MMPs) (Table 1) represent a zinc dependent subset of the protease enzymes. MMP dependent remodeling of the extracellular matrix has been implicated in a variety of human diseases, but is also involved in normal tissue turnover and development. Activity of compounds results from binding to the enzymes in various pockets, such as the P1′ pocket and the P3′ pocket.

MMP compounds in clinical development include batimastat (2) for the treatment of malignant pleural effusion, and marimastat (1) for the treatment of pancreatic cancer. Galardin (3) is for the treatment of corneal ulcers, and a specific MMP-1 inhibitor is RO 31-9790 (4).

Compounds in Clinical Development



(1)



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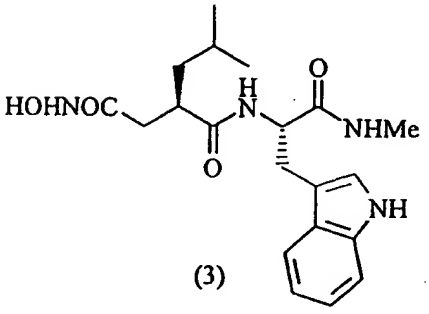

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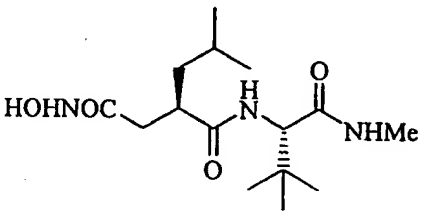

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TABLE 1. MMP-Nomenclature

MMP-1	collagenase-1 (interstitial)
MMP-2	gelatinase A (72kD)
MMP-3	Stromelysin-1
MMP-7	Matrilysin (PUMP)
MMP-8	Neutrophil Collagenase
MMP-9	Gelatinase B (92kD)
MMP-10	Stromelysin-2
MMP-11	Stromelysin-3
MMP-12	metalloelastase
MMP-13	Collagenase-3
MMP-14	MT1-MMP, Membrane-type 1
MMP-15	MT2-MMP, Membrane-type 2
MMP-16	MT3-MMP, Membrane-type 3
MMP-17	MT4-MMP, Membrane-type 4

Succinamides

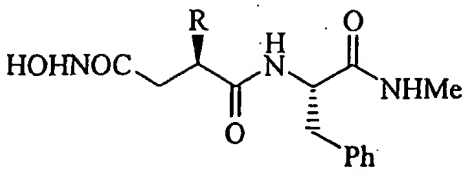
The majority of the MMP inhibitors with the succinic acid template are potent and nonselective, particularly with a hydroxamate zinc binding group. However, it is possible to achieve selectivity with this moiety (Table 2). The series of compounds (**5-10**) are potent against MMP-8, and certain examples (**9,10**) are very potent inhibitors of MMP-9. Selectivity for MMP-3 and MMP-1 can be obtained in this series with the P1′ ligand. The alcohol (**5**) is selective for MMP-1 over MMP-3. The amides (**6**, **7**) and benzyl ether (**8**) are selective for MMP-3 over MMP-1. Compound (**9**) is a potent inhibitor of MMPs 1, 3, 8, and 9. Selectivity for MMP-2 and MMP-3 can be obtained over MMP-1 and MMP-7, when the P1′ substituent is a long chain alkyl group (**11**), in a related series with a carboxylate zinc ligand. The selectivity can be explained by pocket size. Further exquisite selectivity for MMP-2 can be obtained when the chain length is extended. The compound (**12**) is very selective for MMP-2 over MMP-1, 3, and 7.

TABLE 2. MMP Selectivity

Cpd	R = P1′ Group	MMP-1 IC_{50} (μM)	MMP-2 IC_{50} (μM)	MMP-3 IC_{50} (μM)	MMP-7 IC_{50} (μM)	MMP-8 IC_{50} (μM)	MMP-9 IC_{50} (μM)
5	$(CH_2)_4OH$	0.064		2.2		0.007	
6	$(CH_2)_3CONHC_3H_7$	5.1		0.36		0.002	
7	$(CH_2)_3CONH(CH_2)_2Ph$	1.3		0.006		0.032	
8	$(CH_2)_3OCH_2Ph$	2.27		0.043		<0.001	
9	$(CH_2)_4OPh$	0.008		0.028		<0.002	
10	$(CH_2)_5Oph$	0.026		0.014		0.002	0.00031
11	$C_{12}H_{25}$	30% @ 100 μM	0.5	1	10% @ 100 μM		
12	$C_{16}H_{33}$	IA	0.03	10% @ 100 μM	20% @ 100 μM		
13	i-Bu	0.03		3			
14	i-Bu	0.01	0.7	0.008			
15	i-Bu	3.5		0.32	0.07		
16	$-(CH_2)_5-$	0.48		5.9	0.003		
17	$(CH_2)_3Ph$	0.203	0.000062	0.0083			
18	$(CH_2)_3Ph$-4Cl	0.385	<0.00001				0.000016
19	$(CH_2)_3Ph$-4Me	22	0.001	0.47			
20	$(CH_2)_3Ph$-4Me	48	0.0009	0.38			
21	i-Bu	0.1	0.2	9	3	0.4	
22		0.0000025	0.0018	0.023			
23	i-Bu	0.0084		0.0014	0.00014		
24	C_8H_{17}	>10	0.34	0.57			
25	$(CH_2)_2Ph$-4-C_3H_7	5.9	0.0035	0.018			
26	$(CH_2)_2Ph$-4-C_3H_7	>10	0.310	0.068			
27	$(CH_2)_2Ph$	0.72	0.086	0.008			
28	i-Bu	0.02		0.091			0.005
29	i-Bu	0.054		1.4			0.007
30	i-Bu	0.16	>10				0.035
31	i-Bu	0.056	0.178				0.074
32	$(CH_2)_2Ph$-4-C_3H_7	>10	0.0057	0.000036			
33	$NHCOCF_3$	0.040				>1	
34	$NHCOCH_3$	>100					
35	$NHCO(CH_2)_2Ph$	3.5				0.038	
36	NHCObenzotriazole	0.008					0.024
37	$(CH_2)_3Ph$-4Me	17	0.0025	0.277			
38	$(CH_2)_2Ph$	>10	0.02	0.0014			
39	i-Bu	0.0176		0.239			
40		0.38		0.017			
43			0.014	0.017			3.2
44			0.00091	0.0057			0.0015

IA = inactive

Selective Succinate MMP Inhibitors



R

(5) $(CH_2)_4OH$

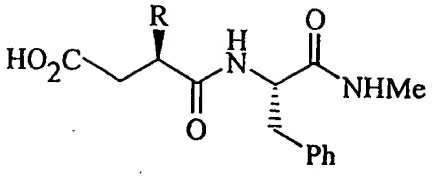
(6) $(CH_2)_3CONHC_3H_7$

(7) $(CH_2)_3CONH(CH_2)_2Ph$

(8) $(CH_2)_3OCH_2Ph$

(9) $(CH_2)_3OCH_2Ph$

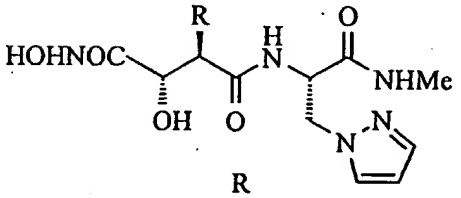
(10) $(CH_2)_4OPh$



R

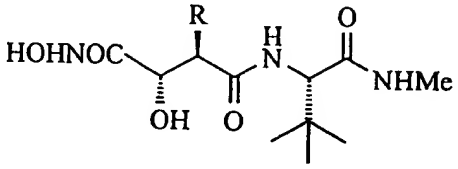
(11) $C_{12}H_{25}$

(12) $C_{16}H_{33}$



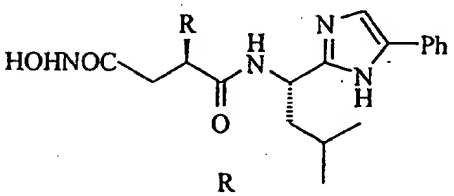
R

(13) ^tBu



R

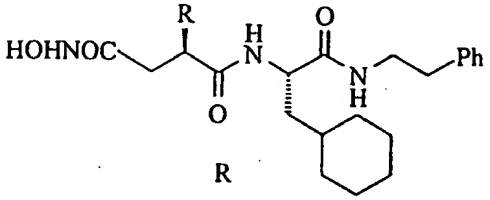
(14) ^tBu



R

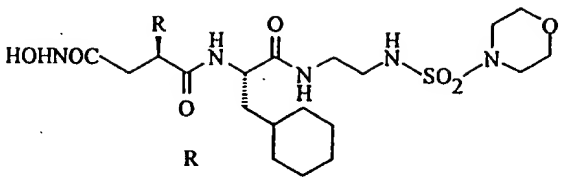
(15) ^tBu

(16) $-(CH_2)_5-$

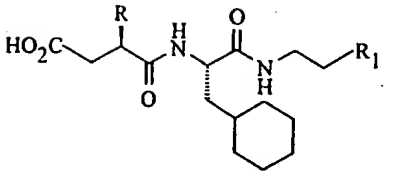


R

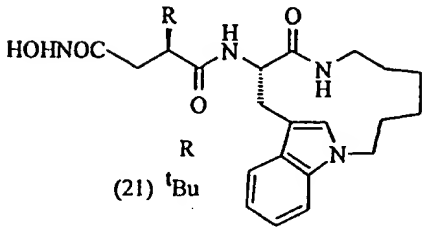
(17) $(CH_2)_3Ph$



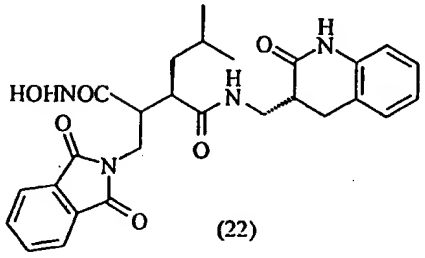
(18) $(CH_2)_3$Ph-4-Cl



	R	R_1
(19)	$(CH_2)_3$Ph-4-Me	Ph
(20)	$(CH_2)_3$Ph-4-Me	$PhSO_2NH_2$



(21) ^{t}Bu



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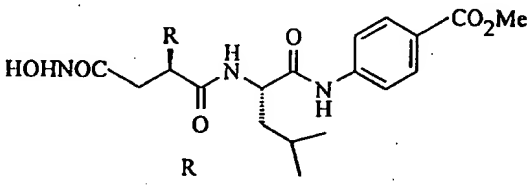


(23) ^{t}Bu

The combination of a small P1′ ligand and a pyrazyl-N-methyl/N-methyl amide at P2-P3′ affords 100-fold selectivity for MMP-1 over MMP-3 (**13**). With tert-butyl at P2′ selectivity for MMP-1 and 3 over MMP-2 is obtained with N-Me amides at P3′ (**14**). MMP-2 potency is restored with P3′ N-phenyl substituents. Compounds selective for MMP-7 over MMP-1 and 3 have been obtained with a bulky P3′ substituent and a small P1′ substituent (**15**). MMP-7 and MMP-1 selectivity can be attenuated with cyclohexyl at P1′ (**16**).

Compounds with 100-fold selectivity for MMP-2 over 3- and 10,000-fold selectivity for MMP-2 over one have been reported by Celltech (**17**). A compound (**18**) from this series also potently inhibits MMP-13. The corresponding carboxylates (**19,20**) also retain this specificity profile. These compounds all contain a cyclohexyl at P2′ and a phenethyl amide, or sulfonamide at P3′.

Modest selectivity for MMPs 1, 2, and 8 over MMP-3 and 7 can be obtained with the analog constrained in the P2′-P3′ region (**21**).

Significant selectivity for MMP-1 over MMP-2 and 3 is observed with the quinolone analog (**22**). These compounds probably bind the same way as compound (**33**), in which the hetero amide group is postulated to occupy P1′ via a conformational expansion of the P1′ pocket.

Modest selectivity for MMP-7 over MMP-1 and 3 is obtained with substituted phenyl amides at P3′ (**23**).

α-Aminocarboxylates

α-Aminocarboxylates are potent MMP inhibitors. A long chain substituent at P1′ yields selectivity for MMP-3 and 2 over MMP-1, with a methyl group at P1 (**24**). A phenethyl moiety substituted para with small alkyl groups also affords compounds that are MMP-3 and 2 selective versus MMP-1 (**25, 26**). Interestingly, selectivity of 100-fold for MMP-3 over -1 and 10-fold over MMP-2 can be achieved with a phthalimidobutyl group at P1 (**27**). A related series of aminocarboxylates developed at Glaxo have selectivity for MMP-1 and 9 over MMP-3. These compounds contain large extended napthalimide groups on the nonprime side. Selectivity over MMP-3 can be attenuated by substitution in the napthalimide ring (**28,29**). A variety of amino acid replacements were tolerated at P2′ by MMP-1 and -9 but good activity for MMP-3 was only found with an aryl side chain. Selectivity for MMP-3 could also be obtained with a non-peptoid substituent at P2′. Phenethyl substitution eliminates MMP-3 activity while benzoic acid substitution retains it (**30,31**).

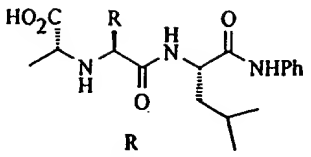
In the related glutamic acids, selectivity for MMP-3 and 2 over MMP-1 is achieved with 4-alkylphenethyl substituents at P1′ (**32**).

Phosphorus/Sulfur Containing Compounds

An intriguing series of compounds in terms of selectivity was published by Glaxo in which an acetamide functionality was postulated to occupy P1′. The thiol compound (**33**) showed selectivity for MMP-1 over 9 as a result of favorable

interactions of the trifluoroacetamide in P1′. The corresponding acetamide (34) did not inhibit MMP-1 presumably as it lacks the capacity to form a fluorine-hydrogen bond. Increased bulk with the phenylethyl amide (35) reversed the selectivity for MMP-9 over MMP-1. However the benzotriazole (36) which would not be expected to fit in P1′ of MMP-1 was an MMP-1 inhibitor. This observation has been reported with phenylethers in P1′, where it was postulated that arg 214 swings out of the way and allows a ð - ð stack between an electron rich phenolic ring and an electron deficient guanidinium ring. A conformational adjustment has been reported recently in the P2′-P3′ region to accommodate hydrophobic inhibitors of MMP-3 and crystal structures of matrilysin have shown the P1′ pocket can expand to accommodate large hydrophobic P1′ substituents. This enzyme flexibility is not surprising given that several of the MMP enzymes can cleave many different natural substrates.

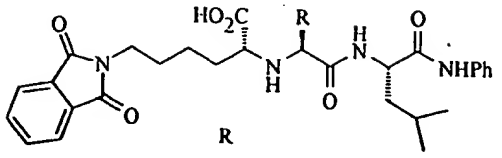
Selective Peptidic MMP Inhibitors



R

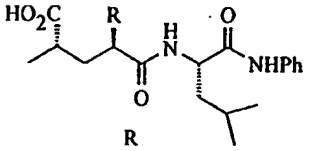
(24) C_8H_{17}

(25) $(CH_2)_2Ph\text{-}4\text{-}C_3H_7$



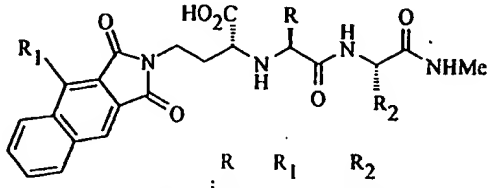
R

(27) $(CH_2)_2Ph$

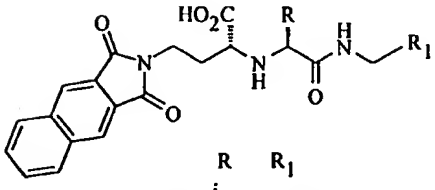


R

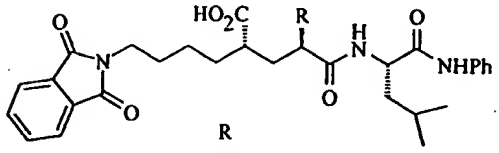
(26) $(CH_2)_2Ph\text{-}4\text{-}C_3H_7$



	R	R_1	R_2
(28)	^iBu	H	CH_2Ph
(29)	^iBu	OMe	CH_2Ph

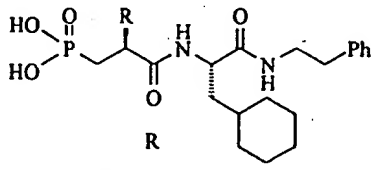


	R	R_1
(30)	^iBu	CH_2Ph
(31)	^iBu	Ph-4-CO_2H



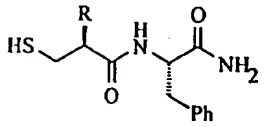
R

(32) $(CH_2)_2Ph\text{-}4\text{-}C_3H_7$



R

(37) $(CH_2)_3Ph\text{-}4\text{-}Me$

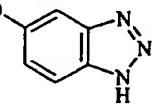


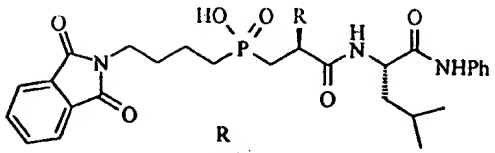
(33) $NHCOCF_3$

(34) NHCOMe

(35) $NHCO(CH_2)_2Ph$

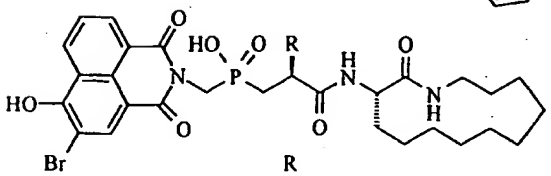
(36) NHCO





R

(38) $(CH_2)_2Ph$



R

(39) ^iBu

The phosphinic acid (37) mirrors the MMP-2 selectivity over MMP-1 and 3 found with the analogous succinamide. This selectivity can be reversed for compound (38) with a P1 substituent and N-phenyl amide at P3′. Bulky P1 substituents and a constrained P2′-P3′ region as exemplified in (39), give rise to MMP-1 selectivity over MMP-3.

Nonpeptidic Inhibitors

Ciba Geigy disclosed a series of aryl sulfonamides of which CGS27023A (40) shows a 20-fold selectivity for MMP-3 over MMP-1. In vivo the compound blocks proteoglycan break down when dosed orally at 30 mg/kg in rabbits injected with stromelysin and is effective in the guinea pig model of osteoarthritis. Related sulfonamides (41) have been disclosed by British Biotech in which the aryl group has been replaced by a long alkyl chain and Pfizer have replaced the picolinyl group with a methylene amide functionality (42). Bayer has disclosed a series of aryl succinic acids in which the usual 2 amino acid residues have been replaced by an aryl moiety. Compounds with phenylalkyl substituents alpha to the acid (43) inhibit MMP-3 and MMP-2 selectively over MMP-9. Inhibition of MMP-9 can also be obtained with a phthalimidoalkyl group á to the carboxylic acid (44). This MMP-9 profile is similar to that observed with α-aminocarboxylates (28-31), thus the phthalimido group presumably occupies the non-prime side. Both compounds (43,44) were active in the guinea pig model of osteoarthritis. In both of these series as with the peptidic SAR most of the activity resides in one stereoisomer suggesting a similar mode of binding. Constrained analogues around the zinc binding region do not increase potency. In vivo, compound (44) was antimetastatic in both a tail vein metastasis model and in a spontaneous metastasis model. Both 43 and 44 were effective in the guinea pig model of osteoarthritis inhibiting femoral lesions 37.8 and 53% respectively.

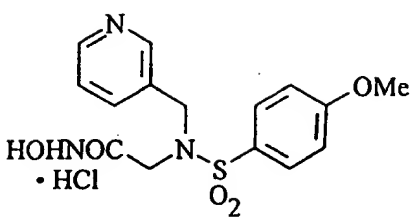
Derivatives of futoenone, exemplified by compound 45 have been shown to weakly inhibit MMPs 1, 3, and 9, with modest selectivity for MMP-3. These compounds are thought to bind on the non-prime side (by overlap modeling with Galardin).

Tetracycline antibiotics, exemplified by aranciamycin (46), are weak inhibitors of MMPs. The MMP activity has been distinguished from antibiotic activity yielding submicromolar MMP-1 inhibitors with the monosaccharide ring deleted (47). Anthracene carboxylic acids (48) have also been reported as MMP-1 inhibitors suggesting the tetracycline D-ring is not needed for MMP activity.

Coumarin derivatives (49) have been shown to be weak inhibitors of MMP-1.

The recent crystallographic publications have provided exquisite insight into the mode of action of peptidic inhibitors with the MMPs. The real situation is more complex than the X-ray/homology models would suggest. It has been noted that the P1′ pockets of the enzymes MMP-3 and MMP-7 are flexible and can breath or change conformation. This is not surprising given that these enzymes, particularly MMP-3 can degrade many natural substrates. Peptidic inhibitors pick up 2 hydrogen bonds per amide, and conformationally these dominate along with Zn coordination. In the case of nonpeptoid inhibitors or simplified peptides which have the propensity to interact hydrophobically, the enzyme may be more accommodating not being constrained in a rigid peptide H-bond framework. Hydrophobic effects would also be amplified with a weaker zinc binding group. Thus expanding the P1′ pocket or changing conformation to take advantage of hydrophobic interactions, seems more likely with a nonpeptidic inhibitor and may possibly give rise to unique selectivities not observed with peptidic inhibitors.

Non-Peptidic MMP Inhibitors



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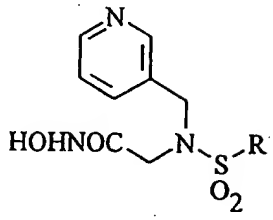

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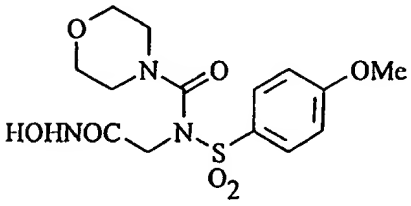
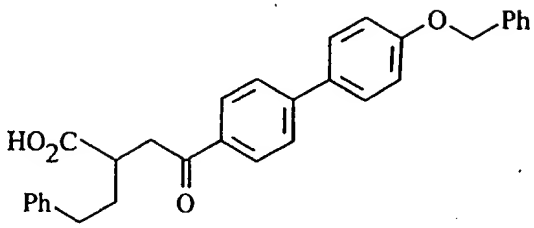
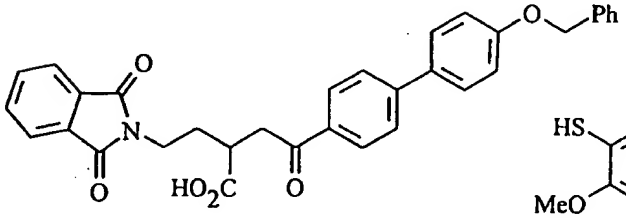


(42)



(43)



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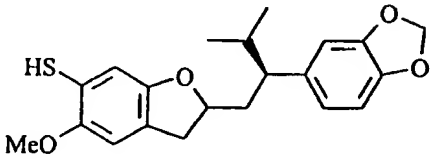

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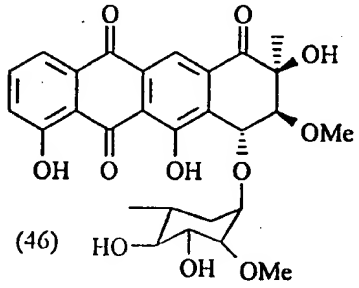
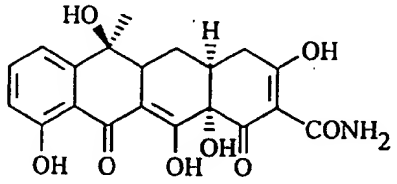


(46)



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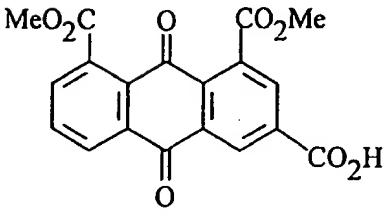

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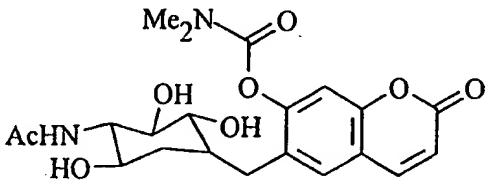


(49)

Matrix Metalloproteinases in Neurological Disorders

Inflammatory diseases can affect the central nervous system (brain and spinal cord); the best characterized of such disorders are multiple sclerosis (MS) and various forms of meningitis and encephalitis. A common feature of these diseases is a breakdown of the blood-brain barrier (BBB) followed by inflammatory perivascular infiltration and eventual demyelination and astrogliosis. MMPs play a key role in allowing inflammatory cells access to the CNS. Both MMP-2 and MMP-9 are found in the CSF of patients with MS and MMP-9 immunoreactivity can be detected in active MS lesions. Similarly, using zymography increased levels of MMP-9 can be found in the cerebrospinal fluid (CSF) of animals with experimental autoimmune encephalitis (EAE). In this commonly used animal model of neuroinflammatory diseases animals are immunized with myelin basic protein or the active epitope of this protein. Further stimulation with pertussis toxin or other endotoxin produces behavioral symptomology ranging from limp tails to complete paralysis. Most animals and humans can be shown to have activated T cells which recognize MBP and other proteins in the myelin sheath, but these cells do not appear to cross the BBB. Direct evidence that MMPs can degrade the BBB and allow infiltration of T cells comes from studies in which MMP-2 has been injected directly in the brain of experimental animals.

The most convincing evidence for the involvement of MMPs in contributing to the breakdown of the BBB and the ensuing inflammation is the ability of hydroxamate inhibitors of MMPs to reduce the clinical symptomology of EAE. Both galardin (GM 6001) and RO 31-9790 have been examined in models of EAE and found to prevent and/or delay the clinical signs. It is clear that the actions of these drugs is occurring after the induction of T cells, since RO 31-9790 has also been shown to protect in a model of adoptively transferred EAE from MBP-sensitized splenocytes. In addition to the role of MMPs in contributing to the breakdown of the BBB there is good evidence that MMPs can also directly degrade myelin basic protein leading to the demyelination characteristic of MS. Using MMPs expressed in Chinese hamster ovary cells, it has been demonstrated that MMP-2 has the greatest activity at digesting MBP, but MMP-9 has also been shown to degrade MBP in an EAE model. This indicates that MMPs play a critical role in two key processes in the

pathophysiology of MS; namely breakdown of the BBB and demyelination. This provides a strong rationale for the development of systemically active inhibitors of MMP-2 and/or MMP-9 in the treatment of multiple sclerosis.

MMPs also play a role in other neurological disorders, which are not generally considered to be inflammatory in nature. For example, MMPs are probably responsible for the opening of the BBB in focal ischemia and hemorrhagic brain injury leading to secondary injury from vasogenic edema. In post mortem tissue from Alzheimer's diseased brain both MMP-2 and MMP-9 have been detected and using zymography the activity of MMP-9 was approximately 4-fold that seen in control brains. â-Amyloid is a potent stimulator of both MMP-2 and MMP-9 in cortical cultures and TIMP staining was found to co-distribute with neuritic lesions and the amyloid precursor protein in Alzheimer's brains. Increased amounts of MMP-9 were also observed in the motor cortex, thoracic, and lumbar cord regions of patients suffering from amyotrophic lateral sclerosis. Taken together these results suggest that MMPs may play a more general role in the degradation of the extracellular matrix in a variety of chronic neurodegenerative disorders.

Wound Healing

Wound healing is characterized by the biosynthesis of normal connective tissue composed of appropriate extracellular and vascular organization and function. This process is dynamic and involves the closely regulated remodeling of ECM by MMPs. Regardless of the wound site, the balance between MMP activity and their endogenous inhibitors is responsible for the establishment of a stable extracellular matrix architecture. However, MMP profiles vary depending on the nature of the injury, wound site, and species. Proteolytic activity within the wound environment is also an important determinant of wound chronicity. In general, excess MMP activity is observed in chronic wounds. Moreover, wound fluid obtained from chronic wounds contains elevated levels of vitronectin and fibronectin degradation products. Factors specific to each class of wound are described below.

Acute Healing Wounds

Collagenase activity is critical for the turnover and restructuring of matrix components during wound repair, and this process appears to be critical for cell movement in the extracellular matrix. Elevation of collagenolytic activity has been reported in association with wound healing. Many cell types have the potential to produce interstitial collagenase, including fibroblasts, macrophages, endothelial cells and neutrophils. Keratinocytes have collagenolytic activity when cultured on certain matrices and in migrating cells during the early phase at the wounds edge. Disruption of the basement membrane appears to be a primary stimulus for induction of MMP-1 expression in keratinocytes. In in vitro systems, keratinocytes migrating on collagen express enhanced collagenolytic activity, whereas contact with laminin does not stimulate collagenolysis. In normal skin, keratinocytes are in contact with laminin and thus are not exposed to collagen. The consistent finding of MMP-1 expression in wound edge epithelium and its close association with keratinocyte migration and re-epithelialization suggest a distinct and temporal role for MMP-1 in wound healing. It appears that MMP-1 contributes to the efficient healing of acute wounds. Indeed, external sources of MMP-1 have been used as a therapeutic approach to promote wound healing.

MMP-2 and 9 are present in healing wounds. The expression of MMP-2 is stable during the first week in healing wounds, with an apparent peak at 4-6 days. The same time at which collagenolytic influences in the wound diminish. Latent and multiple active forms of the active enzyme are present in wound fluid with the two lowest molecular weight forms appearing toward the end of the first week. This temporal sequence is consistent with the appearance of fibroblasts and a decline in macrophages in the wound site. The fibroblasts accumulate near newly formed capillary loops where cell division and deposition of fibrillar collagen occur. Collagen remodeling is a prominent feature during this period and capillaries appear in the wound along with the fibroblasts. Capillary endothelial cells are also a potential source of MMP-2. MMP-9 has also been observed in wound tissues and fluids during the earliest phases of wound repair. MMP-9 is expressed by infiltrating neutrophils, granulation tissue, a few basal layers of the migrating epithelial sheet

and in basal layers in the non wounded area. Most of the enzyme is found in its latent form. However, active enzyme is also present in most instances.

An important consideration regarding the involvement of MMPs in wound healing is the level of endogenous inhibitor present during the healing process. Several studies have shown that the MMP inhibitory activity increases rapidly during the wound healing process. The levels generally reach a peak within the first few days and decline thereafter. Presumably, high levels are required during the early phase of wound healing to temper remodeling during a period of matrix deposition.

Chronic Wounds

Compared with acute wound fluid, total but inactive levels of collagenases are higher in chronic ulcers. Analyzed by immunoblotting/western, immunoreactivities for MMP-1 and MMP-8 are both present. Studies with the MMP-1 inhibitor doxycycline suggest that the dominant enzyme appears to be of the MMP-1 type. Although MMP-1 plays an important role in wound healing, only a few matrix proteins, primarily types 1 and 3 collagen, are cleaved by the enzyme in a wound healing environment.

In order for cleavage of other connective tissue components, including laminin, fibronectin, type IV collagen and glycosaminoglycans, additional proteinase activity is required. MMP-3 and stromelysin-2 (MMP-10) are other metalloproteinases involved in proteolysis and tissue remodeling. MMP-3 is prominently expressed by dermal cells and keratinocytes within chronic wounds. In the dermis, fibroblasts are a major source of the enzyme. In the epidermis, basal cells which are distal to the wound edge, and distinct from those cells producing MMP-1 produce MMP-3. It is likely that the cells which express MMP-3 are those which proliferate and become migrating cells, suggesting that these keratinocytes have distinct roles in tissue remodeling. Because both normal keratinocytes (which do not express MMP-3), and MMP-3 positive keratinocytes are found in contact with basement membrane, the stimulus for enzyme expression is probably due to an interaction with a soluble factor. Stromelysin-2 also has a unique pattern of expression in wound healing.and is produced by basal keratinocytes at the leading

edge of the migrating cells (the same cells which make MMP-1). In contrast with MMP-3, however, a signal for stromelysin-2 is not detected within the dermis. Because stromelysin-2 and MMP-1 are expressed in keratinocytes at the migrating front, contact with the dermal matrix (e.g. collagen) may stimulate release of both enzymes. In addition, stromelysin-2 is not expressed in cells attached to the basement membrane, suggesting that altered cell matrix interactions may stimulate its expression.

Although gelatinase levels are elevated in acute wounds, these enzymes are found in much greater quantities in chronic wounds and ulcers. The levels of MMP-2 are approximately 3-5 fold elevated in chronic wounds, and MMP-9 levels are 5- to 25-fold higher. In addition the local gelatinase profile is not common to all patients and the profiles are much more complex than in acute wound fluid. Several smaller molecular weight bands are detectable in chronic wound fluid consistent with cleavage to smaller activated forms.

The distinct localization of MMP-1, MMP-3 and stromelysin-2 in chronic wounds suggest that the enzymes have different functions. In the dermis, MMP-1 and MMP-3 and the gelatinases affect tissue repair at multiple stages, including remodeling during the formation and removal of granulation tissue and the resolution of scar tissue. In the epidermis, MMP-1 appears to promote keratinocyte migration and promote remodeling of dermal connective tissue. Stromelysin-2 may also facilitate keratinocyte migration by degrading non-collagenous matrix or by removing damaged basement membrane. Stromelysin-2 activates secreted procollagenase but it is unclear whether the enzyme performs this function in vivo. MMP-3 may be useful for restructuring the newly formed basement membrane. Although the over production of MMPs may contribute to wound chronicity, it is also clear that the activity of these enzymes is ultimately beneficial. Therefore, strategies developed for the treatment of chronic wounds with MMP inhibitors must be carefully focused to moderate those mechanisms which prevent healing. The reduction of TIMP-1 and TIMP-2 levels observed in chronic wounds, however, suggests that it might be productive to restore the balance of inhibitory and degradative influences within a chronic wound.

This invention thus provides a method for treating neurological disorders and promoting wound healing by administering an effective amount of an MMP inhibitor. Especially preferred compounds to be utilized include the following:

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-(2-methylpropyl)-γ-oxo-, (S)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-(2-methylpropyl)-γ-oxo-, (R)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-β-(2-methylpropyl)-γ-oxo-, (S);

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-β-(2-methylpropyl)-γ-oxo-, (*R*)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-bromo-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-fluoro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 2′-fluoro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 2′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 2′,4′-difluoro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 3′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-(2-methyl-propyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-bromo-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-fluoro-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-ethyl-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 2′-fluoro-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 2′-chloro-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-methoxy-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 2′,4′-difluoro-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-methyl-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-(2-methyl-propyl)-γ-oxo-4′-pentyl-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-methylene-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 2′-chloro-α-methylene-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-methyl-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-pentyl-;

Benzenebutanoic acid, 4-chloro-α-(2-methylpropyl)-γ-oxo-;

Benzenebutanoic acid, 4-methyl-α-methylene-γ-oxo-;

2-Butenoic acid, 4-(4′-chloro[1,1′-biphenyl]-4-yl)-4-oxo-, (E)-;

2-Butenoic acid, 4-[4-(4-chlorophenyoxy)-phenyl]-4-oxo, (E)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-hydroxy-α-(2-methylpropyl)-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-β-methylene-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-hydroxy-α-(2-methylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-hydroxy-α-(2-methylpropyl)-;

2(3H)-Furanone, 5-(4′-chloro[1,1′-biphenyl]-4-yl)dihydro-3-(2-methylpropyl)-;

2(3H)-Furanone, 5-(4′-chloro[1,1′-biphenyl]-4-yl)dihydro-3-(2-methylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 3′,4′-dichloro-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 3′,5′-dichloro-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(acetyloxy)-γ-oxo-α-(3-phenylpropyl)-;

Benzenepentanoic acid, α-[2-[4-(5-chloro-2-thienyl)phenyl]-2-oxoethyl]-;

2-Furancarboxylic acid, 5-[4-(3-carboxy-1-oxo-6-phenylhexyl)phenyl]-;

Benzenepentanoic acid, α-[2-oxo-2-[4-(3-pyridinyl)phenyl]ethyl]-;

Benzenepentanoic acid, α-[2-oxo-2-[4-[6-(pentyloxy)-3-pyridinyl]phenyl]ethyl]-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′-(pentylthio)-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-methoxy-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 3′-chloro-4′-fluoro-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-ethoxy-γ-oxo-α-(3-phenylpropyl)-;

Benzenepentanoic acid, α-[2-oxo-2-[4-(3-thienyl)phenyl]ethyl]-;

[1,1′-Biphenyl]-4-butanoic acid, 2′,4′-dichloro-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-formyl-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(3-phenylpropyl)-3′,5′-bis(trifluoromethyl)-;

Benzenepentanoic acid, α-[2-oxo-2-[4-(2-thienyl)phenyl]ethyl]-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(3-phenylpropyl)-3′-(trifluoromethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 2′-formyl-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4-hydroxy-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(3-phenylpropyl)-4′-propoxy-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′- (pentyloxy)-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′-(pentyloxy)-α-(3-phenylpropyl)-, (S)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′-(pentyloxy)-α-(3-phenylpropyl)-, (R)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(hexyloxy)-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-butoxy-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′-(3-phenylpropoxy)-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(1-methylethoxy)-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(heptyloxy)-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(cyclohexyl-methoxy)-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(2-methyl-propoxy)-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(3-phenylpropyl)-4′-(2-propenyloxy)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-heptyl-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-decyl-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-nitro-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-cyano-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(2-iodophenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(3-iodophenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(4-iodophenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(3,5-dimethoxyphenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-phenyl-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-(phenylmethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-[(trimethylsilyl)methyl]-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-bromo-γ-oxo- α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, -γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-amino-γ-oxo-α- (2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(2-phenylethyl)-4′-[[(phenylmethoxy)carbonyl]amino]-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-[[(1,1-dimethylethoxy)carbonyl]amino]-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(acetylamino) γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′-[(1-oxopentyl)amino]-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-[(3,3-dimethyl-1-oxobutyl)amino]-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[2-(methoxycarbonyl)phenyl]ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(2-carboxyphenyl)ethyl]-4′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[2-[(diethylamino)carbonyl]phenyl]ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[3-[(diethylamino)carbonyl]phenyl]ethyl]-γ-oxo-, (S)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[3-[(diethylamino)carbonyl]phenyl]ethyl]-γ-oxo-, (R)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[(phenylmethoxy)methyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-(phenoxymethyl)-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(benzoyloxy)- methyl]-5-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-, (1α,2β,5β)-;

1,2-Benzenedicarboxylic acid, 1-[[2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]-methyl]-2-methyl ester,(1α,2β,3α)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[(2-thienylthio)methyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(benzoylamino)methyl]-5-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[[(2-methoxyethoxy)methoxy]methyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[[(phenylmethyl)thio]methyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[(phenylthio)methyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[(propylthio)methyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(2-benzothiazolylthio)methyl]-5-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-, (1α,2β,5β)-;

Benzoic acid, 2-[[[2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl]thio]-, 1-methyl ester, (1α,2β,3α)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[[[(phenylmethoxy)carbonyl]-amino]methyl]-, (1α,2β,5β)-;

Benzoic acid, 2-methyl-, [2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl ester, (1α,2β,3α)-;

Benzoic acid, 3-methyl-, [2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl ester, (1α,2β,3α)-;

Benzoic acid, 4-methyl-, [2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl ester, (1α,2β,3α)-;

Benzoic acid, 2-methoxy-, [2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl ester, (1α,2β,3α)-;

Benzoic acid, 3-methoxy-, [2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl ester, (1α,2β,3α)-;

Benzoic acid, 4-methoxy-, [2-carboxy-3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]cyclopentyl]methyl ester, (1α,2β,3α)-;

Cyclopentanecarboxylic acid, 2-[(2-benzoxazolylthio)methyl]-5-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[(1,3-dihydro-4-nitro-1,3-dioxo-2H-isoindol-2-yl)methyl]-, (1α,2β,5β)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[(1,3-dihydro-5-nitro-1,3-dioxo-2H-isoindol-2-yl)methyl]-, (1α,2β,5β)-;

2H-Benz[f]isoindole-2-butanoic acid, α-[2-(4′-ethoxy[1,1′-biphenyl]-4-yl)-2-oxoethyl]-1,3-dihydro-1,3-dioxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-(acetylamino)-4′-chloro-γ-oxo-;

2H-Isoindole-2-hexanoic acid, α-[2-(4′-chloro[1,1′-biphenyl]-4-yl)-2-oxoethyl]-1,3-dihydro-1,3-dioxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[[[3-(methoxycarbonyl)phenyl]thio]methyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[[(2,6-(dimethylphenyl)thio]methyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[[[4-fluoro-2-(methoxycarbonyl)phenyl]thio]methyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[[[3-[(diethylamino)carbonyl]phenyl]thio]methyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[[[2-[(dimethylamino)carbonyl]phenyl]thio]methyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[[[3-[(dimethylamino)carbonyl]phenyl]thio]methyl]-γ-oxo-;

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, 3-[[4′-(pentyloxy)[1,1′-biphenyl]-4-yl]carbonyl]-, (2-endo,3-exo)-;

1-Cyclopentene-1-carboxylic acid, 5-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-5-[(phenylmethyl)thio]-, (1α,2β,5α)-;

Cyclopentanecarboxylic acid, 2-[(4′-chloro[1,1′-biphenyl-4-yl)carbonyl]-5-[(phenylmethyl)thio]-, (1α,2β,5β)-;

1-Cyclopentene-1-carboxylic acid, 5-[[4′-(pentyloxy)[1,1′-biphenyl]-4-yl]carbonyl]-;

1-Cyclopentene-1-carboxylic acid, 5-[[4′-(hexyloxy)[1,1′-biphenyl]-4-yl)]carbonyl]-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-hydroxy-γ-oxo-α-[(phenylthio)methyl]-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-[2-[(butylamino)carbonyl]phenyl]ethyl]-4′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(3-carboxyphenyl)ethyl]-4′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[3-[(diethylamino)carbonyl]phenyl]ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-[3-[(butylamino)carbonyl]phenyl]ethyl]-4′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[4-[(diethylamino)carbonyl]phenyl]ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-[4-[(butylamino)carbonyl]phenyl]ethyl]-4′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(4-carboxyphenyl)ethyl]-4′-chloro-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-methoxy-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-hydroxy-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-ethoxy-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(2-phenylethyl)-4′-propoxy-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′-(pentyloxy)-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(hexyloxy)-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-butoxy-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(2-phenylethyl)-4′-(phenylmethoxy)-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(3-iodophenyl)ethyl]-γ-oxo-4′-(pentyloxy)-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(3-iodophenyl)ethyl]-γ-oxo-4′-(phenylmethoxy)-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(3-[(diethylamino)carbonyl]phenyl]ethyl]-γ-oxo-4′-(pentyloxy)-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(3-[(diethylamino)carbonyl]phenyl]ethyl]-γ-oxo-4′-(phenylmethoxy)-;

1,2-Pyrrolidinedicarboxylic acid, 3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-, 1-(phenylmethyl) ester, (2*S-trans*)-;

1,2-Pyrrolidinedicarboxylic acid, 3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-, 1-(phenylmethyl) ester, (2′*R-trans*)-;

L-Proline, 3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-1-[[(phenylmethyl)amino]carbonyl]-, *trans*-;

L-Proline, 3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-1-(1-oxo-3-phenylpropyl)-, *trans*-;

L-Proline, 3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-1-(phenylacetyl)-, *trans*-;

L-Proline, 3-[(4′-chloro[1,1′-biphenyl]-4-yl)carbonyl]-1-(3,3-dimethyl-1-oxobutyl)-, *trans*-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-heptyl-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-decyl-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-nitro-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-cyano-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(2-iodophenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(3-iodophenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(4-iodophenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-(3,5-dimethoxyphenyl)ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-phenyl-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-(phenylmethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-γ-oxo-α-[(trimethylsilyl)methyl]-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-bromo-γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(3-phenylpropyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-amino-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-α-(2-phenylethyl)-4′-[[(phenylmethoxy)carbonyl]amino]-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-[[(1,1-dimethylethoxy)carbonyl]amino]-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-(acetylamino)-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, γ-oxo-4′-[(1-oxopentyl)amino]-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-[(3,3-dimethyl-1-oxobutyl)amino]-γ-oxo-α-(2-phenylethyl)-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[2-methoxycarbonyl)phenyl]ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, α-[2-(2-carboxyphenyl)ethyl]-4′-chloro-γ-oxo-;

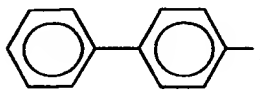
[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[2-[(diethylamino)carbonyl)phenyl]ethyl]-γ-oxo-;

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[3-[(diethylamino)carbonyl)phenyl]ethyl]-γ-oxo-, (*S*)-; and

[1,1′-Biphenyl]-4-butanoic acid, 4′-chloro-α-[2-[3-[(diethylamino)carbonyl)phenyl]ethyl]-γ-oxo-, (*R*)-.

Fenbufen and compounds related to fenbufen can be utilized. Such compounds are described in United States Patent Number 3,784,701 and by

Child, et al., J. Pharm. Sci., 66, 466-476 (1977), and Arzneim-Forsch, 1980, 30(4A):695-702, all of which are incorporated herein by reference. Preferred compounds from the fenbufen series to be utilized in this invention have the formula

 , where R is

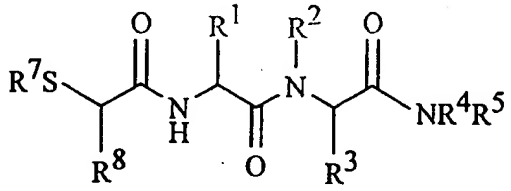
O
‖
CCH_2CH_2COOH (fenbufen), $COCH{=}CHCOOH$, SO_2NH_2, $COCH_2CHCOOH$,
|
CH_3

$COCH_2CH(C_6H_5)COOH$, $COCH_2CH_2SO_3Na$, $CH(OH)CH_2CH_2COOH$,

$COCH_2CHCOOH$, $COCH_2CH_2CONHOH$, $C(=NOH)CH_2CH_2COOH$,
|
OH

and $COCH_2SCH_2COOH$.

Numerous peptides are known matrix metalloproteinase inhibitors. Typical of such peptides are those described in United States Patent Number 5,300,501; 5,530,128; 5,455,258; 5,552,419; WO 95/13289; and WO 96/11209, all of which are incorporated herein by reference. Such compounds are illustrated by the formula



where each of the variable groups can include hydrogen alkyl, aryl, heteroaryl, alkenyl, alkynyl, carboxy, and the like. Preferred compounds from within this class which can be utilized in the method of this invention include the following:

N-[2,3-bis-Acetylmercaptopropanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-3-methoxycarbonylpropanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-4-methoxycarbonylbutanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-5-methoxycarbonylpentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-4-phthalimidobutanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-6-phthalimidohexanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2,3-*bis*-Mercaptopropanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-3-methoxycarbonylpropanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-4-methoxycarbonylbutanyol]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-4-methoxycarbonylpentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-6-methoxycarbonylhexanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-4-phthalimidobutanoyl]-L-leucyl-phenyl-alanine N-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-6-phthalimidohexanyoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-5-methoxycarbonylpentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanyol]-L-valinyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-tryptophan N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-valinyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-tryptophan N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-[β-(4-thiazolyl)]alaine N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-L-(β-(2-pyridyl)alanine N-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-L-leucyl-5-methyl-L-glutamicacid N-methylamide;

N-[2-Acetylmercapto-6-phthalimidohexanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Acetylmercapto-2-(3-phthalimido) phenylacetyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-5-methoxycarbonylpentanoyl]-L-phenylalanine N-methylamide;

N-[2-Mercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-6-methoxycarbonylhexanyol]-L-leucyl-L-trptophan N-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-L-tryptophan N-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-L-[β-(4-thiazolyl)alanine N-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-L-[β-(2-pyridyl)]alanine N-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-L-leucyl-5-methyl-L-glutamic acid N-methylamide;

N-[2-Mercapto-6-phthalimidohexanoyl]-L-leucyl-L-phenylalanine N-methylamide;

N-[N-Mercaptoacetyl)-L-leucyl]-L-phenylalanine N-methylamide;

N-[Acetomercaptoacyl)-L-leucyl-L-phenylalanine methylamide;

(RS)-2-(Acetylthio)pentanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)propanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-3-methylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-2-phenylacetyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-3-phenylpropanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-4-phenylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

N-(Acetylmercaptoacyl)-L-threonyl-L-phenylalanine methylamide;

N-(Acetylmercaptoacyl)-L-leucyl-L-tryptophan methylamide;

(RS)-2-Mercaptopentanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercaptopropanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-3-methylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-2-phenylacetyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-3-phenylpropanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-4-phenylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

N-[N-(Mercaptoacetyl)-L-threonyl]-L-phenylalanine methylamide; and

N-[N-(Mercaptoacetyl)-L-leucyl]-L-tryptophan methylamide.

Additional matrix metalloproteinase (MMP) inhibitors which can be utilized to prevent and treat heart failure include the following:

[4-(N-Hydroxyamino)-2(R)-cyclohexylmethylsuccinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

[4-N-(Hydroxyamino)-2R-isobutylsuccinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-N-[2-(N,N-dimethylamino]ethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-N-[2-(p-sulphonamidophenyl)ethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-N-(2-(p-sulphonylphenyl)ethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-N-[2-(2-pyridyl)ethyl]amide;

[4-(N-Hydroxyamino)-2R-pentylsuccinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

[4-(N-Hydroxyamino)-2R-isoamylsuccinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylbutylsuccinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-N-[3-(4-morpholinyl)propyl]amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-β-cyclohexylalanine-N-[β-alanine]amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-β-cyclohexylalanine amide;

[4-(N-Hydroxyamino)-2R-(3-phenylpropyl)succinyl]-L-β-cyclohexylalanine amide;

[4-(N-Hydroxyamino)-2R-(3-phenylbutyl)succinyl]-L-β-cyclohexylalanine amide;

[4-N-(Hydroxyamino)-2R-phenylethylsuccinyl]-L-leucine-N-(2-phenylethyl)amide;

[4-(N-Hydroxyamino)-2R-phenylpropylsuccinyl]-L-leucine-N-(2-phenylethyl)amide;

[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-L-tryptophan amide;

[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-L-valine amide;

[3-phosphono-2R,S-phenylpropyl-1-oxopropyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide, dimethylester;

[3-Phosphono-2R-phenylpropyl-1-oxopropyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

[3-Phosphono-2S-phenylpropyl-1-oxopropyl]-L-β-cyclohexylalanine-β-alanine;

[3-Phosphono-2R-phenylpropyl-1-oxopropyl]-L-β-cyclohexylalanine;

[3-Phosphono-2S-phenylpropyl-1-oxopropyl]-L-β-cyclohexylalanine-β-alanine, methyl ester;

[3-Phosphono-2R,S-phenylpropyl-1-oxopropyl]-L-β-cyclohexylalanine-N-[4(3-aminopropyl)morpholine]amide, bromine salt;

[3-Phosphono-2R,S-(4-methylphenyl)propyl-1-oxopropyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide, diethylester;

[3-Phosphono-2R,S-(4-methylphenyl)propyl-1-oxopropyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)-amide;

4-t-Butoxy-2(R)-[3-(2-phenoxyethyl)succinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

4-Hydroxy-2(R)-[3-(2-phenoxyethyl)succinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

4-(N-Hydroxyamino-2(R)-[3-(2-phenoxyethyl)succinyl]-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

{4-Hydroxy-2(R)-[3-(4-pyridinium)propyl]succinyl}-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

{4-(N-Hydroxyamino)-2(R)-[3-(4-pyridinium)propyl]succinyl}-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

{4-(N-Hydroxyamino)-2(R)-[3-(N-methyl-4-pyridinium)propyl]succinyl}-L-β-cyclohexylalanine-N-(2-phenylethyl)amide;

{4-Hydroxy-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholine-sulphonylamino)ethyl]amide;

{4-(N-Hydroxyamino)-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide;

{4-(N-Hydroxyamino)-2-(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-morpholinesulphonylamino)ethyl]amide;

{4-N-Hydroxyamino)-2-(R)-[3-(4-methylphenyl)propyl]succinyl}-L-β-cyclohexylalanine-N-[(2-dimethylsulphonylamino)propyl]amide;

[4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillamine]-N-methylamide;

[4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillamine]amide;

[4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-penicillamine]amide;

{4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-[S-(methyl)penicillaminesulphone]-N-methylamide;

{4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-[S-(methyl)penicillaminesulphoxide]-N-methylamide;

{4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-penicillamine-N-methylamide;

[4-(N-Hydroxyamino)-2(R)-3-(2-methylpropyl)succinyl]-L-[S-methyl)penicillamine]-N-methylamide;

N^4-Hydroxy-N^1-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-4-(chlorophenylpropyl)succinamide;

N^4-Hydroxy-N^1-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-(4-methylphenylpropyl)succinamide;

N^4-Hydroxy-N^1-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-(4-methoxyphenylpropyl)succinamide;

N^4-Hydroxy-N^1-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-(4-trifluoromethylphenylpropyl)succinamide;

N^4-Hydroxy-N^1-(1-(S)-carbamoyl-2,2-dimethylpropyl)-2-(R)-(4-chloromethylphenylpropyl)succinamide;

N-[N-(Mercaptoacetyl)-L-leucyl]-L-phenylalanine methylamide;

N-(Acetomercaptoacyl)-L-leucyl]-L-phenylalanine methylamide;

(RS)-2-(Acetylthio)pentanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)propanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-3-methylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-2-phenylacetyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-3-phenylpropanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-(Acetylthio)-4-phenylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

N-(Acetylmercaptoacyl)-L-threonyl-L-phenylalanine methylamide;

N-(Acetylmercaptoacyl)-L-leucyl-L-tryptophan methylamide;

(RS)-2-Mercaptopentanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercaptopropanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-3-methylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-2-phenylacetyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-3-phenylpropanoyl-L-leucyl-L-phenylalanine N-methylamide;

(RS)-2-Mercapto-4-phenylbutanoyl-L-leucyl-L-phenylalanine N-methylamide;

N-[N-(Mercaptoacetyl)-L-threonyl]-L-phenylalanine methylamide;

N-[N-(Mercaptoacetyl)-L-leucyl]-L-tryptophan methylamide;

N-[2,3-*bis*-Acetylmercaptopropanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-3-methoxycarbonylpropanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-4-methoxycarbonylbutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-5-methoxycarbonylpentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-4-phthalimidobutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-6-phthalimidohexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2,3-*bis*-Mercaptopropanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-3-methoxycarbonylpropanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-4-methoxycarbonylbutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-5-methoxycarbonylpentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-4-phthalimidobutanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-6-phthalimidohexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-5-methoxycarbonylpentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-*L*-valinyl-*L*-phenylalanine N-methylamide;

N-[2-Acetylmercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-tryptophan *N*-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-valinyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-tryptophan *N*-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-[β-(4-thiazolyl)]alanine *N*-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-[β-(2-pyridyl)]alanine *N*-methylamide;

N-[2-Acetylmercapto-5-phthalimidopentanoyl]-*L*-leucyl-5-methyl-*L*-glutamic acid *N*-methylamide;

N-[2-Acetylmercapto-6-phthalimidohexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Acetylmercapto-2-(3-phthalimido)phenylacetyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-5-methoxycarbonylpentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-6-methoxycarbonylhexanoyl]-*L*-leucyl-*L*-tryptophan *N*-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-tryptophan *N*-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-[β-(4-thiazolyl)alanine *N*-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-*L*-[β-(2-pyridyl)]alanine *N*-methylamide;

N-[2-Mercapto-5-phthalimidopentanoyl]-*L*-leucyl-5-methyl-*L*-glutamic acid *N*-methylamide;

N-[2-Mercapto-6-phthalimidohexanoyl]-*L*-leucyl-*L*-phenylalanine *N*-methylamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(3-picolyl)amino]-3-methylbutanamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-3-picolyl)amino]-2-cyclohexylacetamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(benzyl)amino]-4-methylpentanamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(benzyl)amino]-6-[(N,N-dimethylglycyl)amino]hexanamide hydrochloride;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(3-picolyl)amino]-3-methylbutanamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(4-picolyl)amino]-2-cyclohexylacetamide;

N-Hydroxy-2(R)-[(4-methoxybenzenesulfonyl]-(4-picolyl)amino]-2-(2-tetrahydrofuranyl)acetamide;

N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl]-(3-picolyl)amino]-3-methylbutanamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-thiophenylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-thiobenzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylacetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-isopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-thioacetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-thioisopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl thio-tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl acetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylisopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthioacetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthioisopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methylthio-tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-hexyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methoxyphenylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methoxybenzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-(methylthio-2-thienyl)succinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-benzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methyl acetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylisopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methyl-tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylthioacetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylthioisopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-ethylphenyl-3S-methylthio-tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthiophenylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthiobenzylsuccinyl]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthio-2-thienyl)succinyl]-N^1-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl acetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylisopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthioacetate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthioisopropanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methylthio-tert-butanoate]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl-(2-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl-(3-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-octyl-3S-methyl-(4-pyridyl)]-N^2-(S)-piperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-4'(S/R)-benzylpiperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-5'(S/R)-benzylpiperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-6'(S/R)-benzylpiperazic acid N-methyl amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-N^2-(S)-[5',6']benzopiperazic acid N-methyl amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-isobutylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-hexylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-heptylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-octylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-ethylphenylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-propylphenylclycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethylthiobenzyl]-α-(S)-isobutylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethylthiobenzyl]-α-(S)-hexylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethylthiobenzyl]-α-(S)-ethylphenylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethylthiobenzyl]-α-(S)-propylphenylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyloxybenzyl]-α-(S)-isobutylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyloxybenzyl]-α-(S)-hexylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyloxybenzyl]-α-(S)-ethylphenylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-ethyloxybenzyl]-α-(S)-propylphenylglycine-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxy-4-(p-toluenesulfonyl)butyl]-α-(S)-phenethylglycyl-(S)-N^2-piperazic acid methyl amide;

N-[1(R)-Carboxyethyl]-α-[2-(4-phenylphenoxy)ethyl]-glycyl-(S)-N^2-piperazic acid methyl amide;

2-[2(R)-[2-[1,1′-Biphenyl)yl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[1,1′-Biphenyl)yl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[1,1′-Biphenyl)yl]propyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-(4-Propylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-(4-Butylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-(4-t-Butylphenyl)ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[4-(4-Fluorophenyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[4-(4-Fluorophenyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-n-Octyl-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Thiazolyl)phenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Oxazolyl)phenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[4-(Dimethylamino)methylphenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[4-(Dimethylamino)methylphenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[4-(Dimethylamino)methylphenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[4-(Dimethylamino)methylphenyl]ethyl]-4-(3-phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Imidazolyl)phenyl]ethyl]-4-butyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Imidazolyl)phenyl]ethyl]-4-methyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Imidazolyl)phenyl]ethyl]-4-[3-(phenylsulfonyl)propyl-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

2-[2(R)-[2-[(4-Imidazolyl)phenyl]ethyl]-4-[3-(phenylpropyl)-4(S)-carboxy-1-oxobutyl]-3(S)-methylaminocarbonyl-hexahydropyridazine;

$HS(CH_2)_2$-(S-*D*-Leu)-Phe-NHMe;

HS(*S*)$CHMeCH_2$-(S-*D*-Leu)-Phe-NHMe;

HS(*S*)CH(PhtNBu)CH_2-(S-*D*-Leu)-Phe-NHMe;

HS(*S*)CH(PhtNEt)CH_2-(S-*D*-Leu)-Phe-NHMe;

HS(1,2-cyclopentyl)(S-*D*-Leu)-Phe-NHMe

Me-$S(NH)_2$-(CH_2-DL-Leu)-Trp-NHBn;

n-Bu-$S(NH)_2$-(CH_2-DL-Leu)-Trp-NHBn;

n-Bu-$S(NH)_2$-(CH_2-DL-TyrOCH_3)-Trp-NHBn;

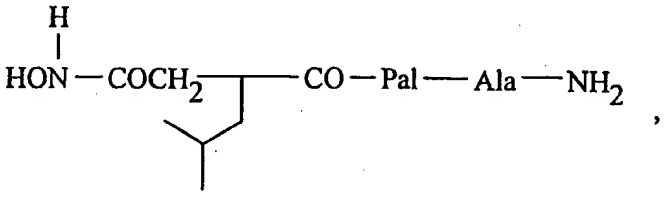
Me-RS-SO(NH)-(CH_2-L-Leu)-Phe-Ala-NH_2;

n-Bu-RS-SO(NH)-(CH_2-L-Leu)-Phe-Ala-NH_2;

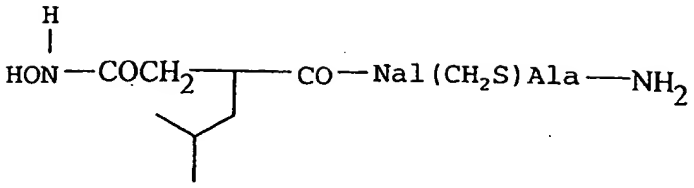
HONH-C-$CH_2CH(CH_2CH(CH_3)_2)$-CO-Nal-Ala-NH_2;

HO-NH-CO-CH_2-CH-(CH_2-$CH(CH_3)_2$-CO-Nal-Pro-NH_2;

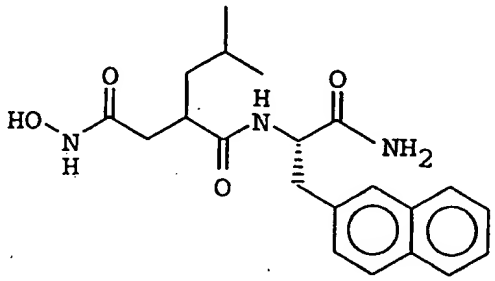
HO-NH-CO-$CH(CH_3$-$CH(CH_2)$-$CH(CH_3)_2$)-CO-Nal-Ala-NH_2;

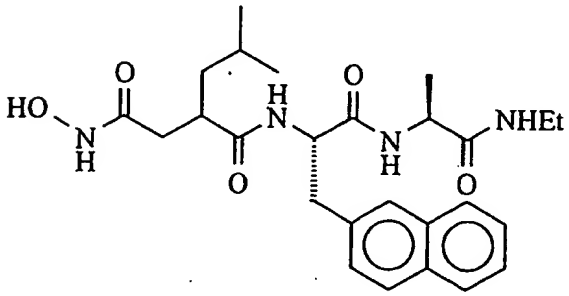


wherein Pal is 3-pyridylalanine;



HO-NH-CO-CH_2-CH(CH_2CH(CH_3)$_2$)-CONal-(CH_2NH)-Ala-NH_2;





4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(2-morpholin-4-ylethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[methylamino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1H-imidazol-2-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1H-tetrazol-5-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[(2-(phenyl)ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(pyridin-3-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(2-methyl-2H-tetrazo-5-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(4-hydroxy-2-methyl-pyrimidin-5-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[2-(2-pyridin-3-yl)ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[1-(1H-tetrazol-5-yl)ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(5-amino-4H-[1,2,4]-triazol-3-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[1-(6-oxo-1,6-dihydro-pyridazin-3-yl)ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(phenyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(pyridin-4-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[2-(1H-imidazol-4-yl)ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(pyridin-2-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(4-sulfamoyl-phenyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-sulfamoyl-phenyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(4-dimethylamino-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[1-(S)-phenyl-ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1,1-dioxo-tetrahydro-thiophen-3-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(4-sulfamoyl-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[1-(R)-phenyl-ethyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-fluorobenzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(furan-2-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1-methyl-1H-tetrazol-5-ylmethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1,2,3,4-tetrahydro-naphthalen-1-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(2,4-difluoro-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-nitrobenzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(4-nitrobenzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(4-methanesulfonylamino-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-methanesulfonylamino-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3,4-difluoro-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-trifluoromethyl-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-[2-(S)-[1-(R)-Carboxy-3-(1,3-dioxo-1,3-dihydro-benzo[f]isoindol-2-yl)-propylamino]-4-methyl-pcentanoylamino-methyl)-benzoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(2-hydroxy-1,1-bis-hydroxymethyl-ethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3,5-difluoro-benzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[benzylmethyl-amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(2-dimethylaminoethyl)-methyl-amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1-azabicyclo[2.2.2]-oct-3(R)-amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1-azabicyclo[2.2.2]oct-3-(S)-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-(R)-4-(S)-5-(R)-6-tetrahydrox-tetrahydra-pyran-2-(R)-ylmethyl)amino]-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(N,N'-dimethyl-hydrazino)carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(methylmethoxy)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(dimethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(2-oxo-tetrahydro-thiophen-3-(R)-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(2-oxo-tetrahydro-thiophen-3-(S)-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-(R)-acetylamino-4-(S)-5-(S)-dihydroxy-6-(R)-hydroxymethyl-tetrahydro-pyran-2-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[benzyl(2-hydroxyethyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[3,4-dihydro-1H-isoquinoline-2-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[4-methylpiperazine-1-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[1-oxo-[1,4]thiazinane-4-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[morpholine-4-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[4-(2-3-dihydroxy-propyl)-piperazine-1-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[3,4,5,6-tetrahydro-H-[2,3]bipyridinyl-1]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1-methyl-8-oxo-1,7-diazacyclotridec-9-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[methyl-1-methyl-piperidin-4-yl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(4-hydroxy-1,1-dioxo-tetrahydro-thiophen-3-yl)amino]carbonyl]butyl]-amino]-butanoic acid;

4-(1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-(4-ethoxycarbonylmethyl-piperazine-1-carbonyl)butyl]amino]-butanoic acid;

4-(1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(1,1-dioxo-tetrahydro-thiophen-3-yl)-methyl-amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[2-(R)-(pyridin-3-yl)-pyrrolidinecarbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[2-(S)-(pyridin-3-yl)-pyrrolidinecarbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[3-oxo-2-(R)-phenyl-piperazine-1-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[3-oxo-2-(S)-phenyl-piperazine-1-carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[(pyridine-3-carbonyl-hydrazino)carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(benzenesulfonyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(3-aminobenzyl)amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[4-(trifluoro-methanesulfonylamino)benzyl]amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[2-hydroxy-(R)-bicyclo[4.3.0]nona-3,6(1)-diene]amino]carbonyl]butyl]-amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[[2-hydroxy-(S)-bicyclo[4.3.0]nona-3,6(1)-diene]amino]carbonyl]butyl]-amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[[(N-methyl-pyrrolidine)-methyl-amino]carbonyl]butyl]amino]-butanoic acid;

4-(1,3-Dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl)-2-(R)-[[3-methyl-1-(S)-[(N-ethoxycarbonylmethyl-piperazine)-1-carbonyl]butyl]amino]-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-bromo-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-propoxy-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-amino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-methyl-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-phenyl-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-methanesulfonylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-benzenesulfonylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[1-(S)-(Benzylamino)carbonyl-3-methylbutylamino]-4-(5-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butanoic acid;

2-(R)-[[3-Methyl-1-(S)-[[(pyridin-3-ylmethyl)amino]carbonyl]-butyl]amino]-4-(1,3,5,7-tetraoxo-3,5,6-tetrahydro-1H-pyrolo[3,4-f]isoindol-2-yl)butanoic acid;

EtONHCONMe-CH_2CH(iBu)-CO-L-Trp-NHEt;

EtCONOH-CH_2CH(iBu)-CO-L-Trp-NHEt;

n-PrCONOEt-CH_2CH(iBu)-CO-L-Trp-NHEt;

EtNHCONOMe-CH_2CH(iBu)-CO-L-Trp-NHEt;

MeNHCONOH-CH_2CH(iBu)-CO-L-Trp-NHEt;

EtONHCONMe-CH_2CH(iBu)-CO-L-Ala(2-naphthyl)-NHEt;

EtCONOH-CH_2CH(iBu)-CO-L-Ala(2-naphthyl)-NHEt;

n-PrCONOEt-CH_2CH(iBu)-CO-L-Ala(2-naphthyl)-NHEt;

EtNHCONOMe-CH_2CH(iBu)-CO-L-Ala(2-naphthyl)-NHEt;

MeNHCONOH-CH_2CH(iBu)-CO-L-Ala(2-naphthyl)-NHEt;

HONHCONHCH$_2$CH(iBu)-CO-L-TrpNHMe;

HONHCONHCH$_2$CH$_2$CH(iBu)-CO-L-TrpNHMe;

HONHCONHCH(iBu)-CO-L-TrpNHMe;

H_2NCON(OH)CH(iBu)-CO-L-TrpNHMe;

N(OH)CH_2CH(iBu)-CO-L-TrpNHMe;

H_2NCON(OH)CH_2CH_2CH(iBu)-CO-L-TrpNHMe;

CH_3CON(OH)CH(iBu)-CO-L-TrpNHMe;

CH_3CON(OH)CH_2CH(iBu)-CO-L-TrpNHMe;

CH_3CON(OH)CH_2CH_2CH(iBu)-CO-L-TrpNHMe;

NHOHCOCH$_2$CH(i-Bu)CO-L-Trp-NHMe;

HONHCONHCH$_2$CH(i-Bu)CONHCHCOOH or

R^4

ROOCCH$_2$CH(i-Bu)CONHCHCOOH;

R^4

N-{D,L-2-(Hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-(2'-naphthyl)alanyl-L-alanine, 2-(amino)ethyl amide;

N-{D,L-2-(Hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine, 2-(amino)ethyl amide;

4(S)-[3-Hydroxyaminocarbonyl-2(R)-(2-methylpropyl)propanoyl]amino-1,2,3,4,5-tetrahydro-3H-2-benzazepin-3-one;

[4-(N-Hydroxyamino)-(2R)-isobutyl-3-methylsuccinyl]-L-phenylglycine-N-methylamide;

4(S)-[2(R)-[1(R)-Hydroxycarbamoyl-2-morpholinoethyl]-4-methylvaleryl]amino-1,2,4,5-tetrahydro-3H-2-benzazepine-3-one;

(1R,4S)-4-[(2R)-Hydroxycarbamoylmethyl-4-methylvaleryl]amino-3-oxo-1,2,4,5-tetrahydro-3H-2-benzazepine-1-carboxylic acid;

3-[2-(N-Methylcarbamoyl)ethylsulfinyl]-5-methylhexanohydroxamic acid;

N-[(2-Thenoylmercapto-3-methyl)-butanoyl]-homocysteine thiolactone;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-isoleucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-alanine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-phenylalanine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-serine-O-benzyl ether, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-tryptophan, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-α-(S)-(2-phenyl-ethyl)glycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-norleucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-valine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-serine, N-phenylamide hydrochloride;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-asparagine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-threonine, N-phenylamide hydrochloride;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-lysine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-glutamic acid, N-phenylamide;

N-[1(R)-carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-tyrosine, N-phenylamide hydrochloride;

N-[1(R)-Carboxy-5-(1,3-dioxo-isoindolin-2-yl)pentyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-5-(1-oxo-isoindolin-2-yl)pentyl]-α-(S)-(2-phenyl-ethyl)-glycine-(S)-leucine, N-phenylamide hydrochloride;

N-[1(R)-Carboxy-5-(1-oxo-isoindolin-2-yl)pentyl]-α-(S)-(2-phenyl-ethyl)-glycine-(S)-arginine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-(3-hydroxyphenyl)-ethyl)glycine-(S)-leucine, N-phenylamide hydrochloride;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-(4-methylphenyl)-ethyl)glycine-(S)-leucine, N-phenylamide hydrochloride;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-(2′-thienyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-(4-ethylphenyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-5-(1-oxo-isoindolin-2-yl)pentyl]-α-(S)-(2-(4-propylphenyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-(4-chlorophenyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-α-(S)-(2-cyclohexyl-ethyl)glycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-α-(S)-(cyclohexyl)glycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-α-(S)-(cyclohexylmethyl)glycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-β-naphthylalanine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-α-naphthylalanine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-[(L)-glutamic acid, α,L-bis-N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-cyclohexylamide;

N-[(1(R)-Carboxy-ethyl)]-α-(S)-(2-phenyl-ethyl)glycine-α-(S)-(4-hydroxyphenyl-ethyl)glycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-phenylglycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-glutamic acid, N_L-benzylamide, N_α-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-ornithine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-arginine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-α-(S)-(3-phenylpropyl)glycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-α-(S)-n-octylglycine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-(4-carboxyphenyl)amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-(4-trifluoromethylphenyl)amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-(3-pyridyl)amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-phenyl-ethyl)glycine-(L)-leucine, N-(benzothiazol-2-yl)amide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-(4-n-propylphenyl)ethyl)glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-4-propylphenyl)ethyl)glycine-(L)-arginine, N-phenylamide;

N-[1(R)-Carboxy-ethyl]-α-(S)-(2-(3,4-dimethylphenyl-ethyl)glycine-(L)-leucine, N-phenylamide;

(2-(((4-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-butyl)hydroxyphosphinyl)methyl)-4-phenylbutanoyl)-L-leucine, N-phenylamide;

(2-(((4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-butyl)hydroxyphosphinyl)methyl)-4-phenylbutanoyl)-L-leucine, N-phenylamide;

(2-(((4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)butyl)(2-methyl-1-(1-oxopropoxy)propoxy)phosphinyl)methyl)-4-phenylbutanoyl)-L-leucine, N-phenylamide;

(2-((Hydroxy(methyl)phosphinyl)methyl)-4-phenylbutanoyl)-L-leucine, N-phenylamide;

[[Hydroxy[1(R)-[N-(N-acetyl-L-prolyl-L-alanyl)-amino]-ethyl]-phosphinyl]-methyl]-4-phenyl-butanoyl-L-leucyl, N-phenylamide;

[Hydroxy-[N-(N-(benzoyl)-L-prolyl)aminobutyl]phosphinyl]methyl]-4-phenyl-butanoyl-L-leucine, N-phenylamide;

[Hydroxy-[2-Methylpropyloxycarbonyl-aminobutyl]-phosphinyl]methyl]-4-phenylbutanoyl-L-leucine, N-phenylamide;

[Hydroxy-[1-Methylethylaminocarbonyl-aminobutyl]-phosphinyl]methyl]-4-phenylbutanoyl-L-leucine, N-phenylamide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucinamide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucine, N-phenylamide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucine, N-benzylamide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-leucine, N-(2-phenylethyl)amide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalaninamide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalanine N-phenylamide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalanine N-benzylamide;

N-(2-Thiomethyl-4-phenylbutanoyl)-(L)-phenylalanine-b-alanine;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(2(S)-t-butyl)glycine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(2(S)-t-butyl)glycine, N-(4-pyridylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(L-arginine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(2(S)-t-butyl)glycine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(2(S)-(4-thiazolylmethyl)glycine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(2(S)-(3-pyridylmethyl)glycine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, N-(4-pyridyl)amide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(2(S)-(2-pyridylmethyl)glycine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-arginine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-phenylalanine, N-4-pyridylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(1-(4-(N-(2-oxoisoindolinyl))-butyl))-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(1-(4-(N-(2-oxoisoindolinyl))-but-2-enyl))-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(4-Fluorophenyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(Phenyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(4-Methoxyphenyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, phenylamide)amide;

2(R)-(2-(4-(4-Methylphenyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, phenylamide)amide;

2(R)-(2-(4-(4-Hydroxy-n-butyl)-phenyl)-ethyl)-4-methylpentanedioic acid 1-(S-leucine, phenylamide)amide;

2(R),4(S)-(2-(4-(3-Hydroxy-n-propyl)phenyl)ethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-Phenylethyl)-4-methyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(L-leucine, N-ethylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-(L-leucine, N-isopropylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)propyl)-1,5-pentanedioic acid 1-(2(S)-tert-butyl-glycine, N-4-pyridyl)amide)amide;

2(R)-(3-(4-(1-n-Propyl)phenyl)propyl)-1,3-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-hexyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-butyl-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(3-methylbenzyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(2-benzimidazolyl)butyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(2-benzthiazolyl)butyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(2-benzoxazolyl)butyl)-1,5-pentanedioic acid 1-(L-leucine, N-phenylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-phenylamide)amide 9-piperidineamide;

2(R)-(2-(4-(1-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-phenylamide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-tert-butylamide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-benzylamide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-morpholineamide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(1(R)-phenylethyl)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(1(S)-phenylethyl)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(N-methyl-N-phenyl)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(N'-methylpiperazine)amide trifluoroacetic acid salt;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide 9-(3-pyridyl)amide;

2(R)-(2-(4-(1-Propyl)phenyl)ethyl)-4-carboxy-1,9-nonanedioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-((R)-(S-p-methoxybenzyl)penicillamine, N-phenylamide)amide;

2(R)-(2-(4-(1-Propyl)phenyl)ethyl)-1,5-pentanedioic acid 1-((R)-(S-p-methoxybenzyl)penicillamine sulfone, N-phenylamide)amide;

2-(2-(4-(1-Propyl)phenyl)ethyl)-4-(1-(4-(2-phthalimido))butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-benzoylamino-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-pivaloylamino-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-phenylsulfonylamino-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(N'-phenylureido)-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-phenyloxycarbonylamino-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-N'-benzyloxycarbonylamino-L-prolylamino)-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-cyclopentylamino-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-(2-carboxybenzoylamino)-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-methylamide)amide;

2(R)-(2-(4-(1-n-Propyl)phenyl)ethyl)-4-(4-cyano-1-butyl)-1,5-pentandioic acid 1-(L-leucine, N-phenylamide)amide;

N-[1(R)-Carboxyethyl]-α-(S)-(9-amino-n-nonyl)]glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxyethyl]-α-(S)-(n-octyl)]glycine-(L)-leucine, N-phenylamide;

N-[1(R)-Carboxyethyl]-α-(S)-(n-octyl)]glycine-(L)-arginine, N-phenylamide;

N-[1(R)-Carboxyethyl]-α-(S)-(9-amino-n-nonyl)]glycine-(L)-arginine, N-phenylamide;

N-[1(R)-Carboxyethyl]-α-(S)-(n-decyl)]glycine-(L)-leucine, N-phenylamide;

1-(2-(4-Propylphenyl)ethyl)cyclopentane-1,3-dicarboxylic acid 1-(L-leucine, N-phenylamide)amide;

1-(2-(4-Propylphenyl)ethyl)cyclohexane-1,3-dicarboxylic acid 1-(L-leucine, N-phenylamide)amide;

N-[1(R)-Carboxyethyl]-α-(S)-2-(4-fluorobiphenyl)-glycyl-(S)-2-(*tert*-butyl)glycine, N-phenylamide;

3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxy-3,4-dihydrocarbostyril;

3S-[4-(N-Hydroxyamino)-2R-isobutyl-3S-acetylthio-methylsuccinyl]amino-3,4-dihydrocarbostyril;

3S-[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]amino-1-methoxy-3,4-dihydrocarbostyril;

3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxymethyl-3,4-dihydrocarbostyril;

1-Carboxymethyl-3S-[4-N-hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]amino-3,4-dihydrocarbostyril;

3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxyethoxymethyl-3,4-dihydrocarbostyril;

3S-[4-(N-Hydroxyamino)-2R-heptylsuccinyl]amino-1-methoxy-3,4-dihydrocarbostyril;

7-Chloro-3S-[4-(N-hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxymethyl-3,4-dihydrocarbostyril;

3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxyethyl-3,4-dihydrocarbostyril;

3S-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxyethyl-6,7-methylenedioxy-3,4-dihydrocarbostyril;

3R-[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]amino-1-methoxyethyl-6,7-methylenedioxy-3,4-dihydrocarbostyril;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl) (3-morpholin-4-yl-3-oxopropyl)amino]-3-methyl-butyramide;

2-(R)-2-[(2-Benzylcarbamoylethyl)(4-methoxy-benzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl) (2-[(pyridin-3-ylmethyl)carbamoyl]ethyl)amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-([4-methoxybenzenesulfonyl]-[2-(methylpyridin-3-ylmethylcarbamoyl)ethyl]amino)-3-methylbutyramide;

4-(3-[1-(R)-1-Hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)amino]propionyl)piperazine-1-carboxylic acid, tert-butyl ester;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperazin-1-ylpropyl)amino)-3-methylbutyramide hydrochloride;

2-(R)-2-[(Benzylcarbamoylethyl)(4-methoxy-benzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl][(2-morpholin-4-ylethylcarbamoyl)methyl]amino]-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl) ([(pyridin-3-ylmethyl)carbamoyl]methyl)amino)-3-methylbutyramide;

2-(R)-3,3,3,-Trifluoro-N-hydroxy-2-[(methoxy-benzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]propionamide;

2-(R)-N-Hydroxy-2-((4-phenoxybenzenesulfonyl)[2-methylpyridin-4-ylmethylcarbamoyl)ether]amino)-3-methylbutyramide;

4-[4-Methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-1-methylpiperidene-4-carboxylic acid hydroxyamide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]amino)-3-methylbutyramide;

2-(R)-2-[(2-Carboxyethyl)(4-methoxybenzene-sulfonyl)amino]-N-hydroxy-3-methylbutyramide;

[(2-Carboxyethyl)(3,4-dimethoxybenzene-sulfonyl)amino]-N-hydroxy-acetamide;

2-(R)-2-[(2-Carbamoylethyl)(4-methoxybenzene-sulfonyl)amino]-N-hydroxy-3-methylbutyramide;

2-(R), 3-(R)-3, N-Dihydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperidin-1-ylpropyl)amino]-butyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)[3-(methylpyridin-3-ylmethylcarbamoyl)propyl]amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)-[2-(methylcarboxymethylcarbamoyl)ethyl]amino)-3-methyl-butyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)[(1-methylpiperidin-4-ylcarbamoyl)methyl]amino)-3-methylbutyramide;

2-(R)-N-Cyclohexyl-N-hydroxy-2-((4-methoxy-benzenesulfonyl)-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]amino)-acetamide;

2-(R)-N-Hydroxy-2-[(methoxybenzenesulfonyl)(3-morpholin-4-yl-[3-oxopropyl)amino]-4-(morpholin-4-yl)butyramide;

[4-N-Benzyloxyamino)-2(R)-isobutylsuccinyl]-L-leucyl-L-alanine ethyl ester;

[4-N-Benzyloxyamino)-2(R)-isobutylsuccinyl]-3(RS)-aminolaurolactam;

N^a-[4-(N-Benzyloxyamino)-2(R)-isobutylsuccinyl]-N^e-(N-benzyloxycarbonylglycyl)-L-lysyl-L-alanine ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine isopentylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-valylglycine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine ethylamide;

N^a-[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-N^e-tert.butoxycarbonyl-L-lysylglycine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-O-methyl-L-tyrosinylglycine ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-O-methyl-L-tyrosinylglycine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucyl-L-alanine ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine isopentyl ester;

[4-(N-Hydroxyamino)-2(R)-propylsuccinyl]-L-leucylglycine ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-sec.butylsuccinyl]-L-leucylglycine ethyl ester;

[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-L-leucyl-L-alanine;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylglycine methyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucylsarconsine ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucyl-L-proline ethyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucine-L-alanine isopropyl ester;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucine-2-oxopropylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucine-2-methoxyethylamide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-leucine-2,2-dimethoxyethylamide;

N^a-[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-N^e-glycyl-L-lysine methylamide;

N^a-[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-N^e-(4-carboxybenzoyl)-L-lysl-L-alanine ethyl ester;

N^a-[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-N^e-(4-carboxybenzoyl)-L-lysyl-L-aline;

[4-(N-Hydroxyamino)-2(R)-isobutylsuccinyl]-3(RS)-aminooctahydro-2H-azonin-2-one;

[4-(N-Hydroxyamino)-3(S)-methyl-2(R)-isobutyl-succinyl]-L-leucylglycine ethyl ester;

[(3-Aminophthalimido)methyl][(RS)-4-methyl-2-[[(S)3-methyl-1-(methylcarbamoyl)butyl]carbamoyl]pentyl]phosphinic acid;

[(RS)-4-Methyl-2-[[(S)-3-methyl-1-(methyl-carbamoyl)butyl]carbamoyl]-pentyl](1,8-naphthalenedicarboximidomethyl)-phosphinic acid;

[(R or S)-4-Methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]-pentyl](1.8-naphthalenedicarboximidomethyl)phosphinic acid;

N-[N-[(R or S)-2[[[[[N-[1-(Benzyloxy)carbonyl]-L-prolyl]-L-leucyl]amino]methyl]hydroxyphosphinyl]-methyl]-4-methylvaleryl]-L-leucyl]-L-alanine;

[[1,4-Dihydro-2,4-dioxo-3(2H)-quinazolinyl]-methyl][[(R or S)-4-methyl-2-[[(R or S)-2-oxo-3-azacyclotridecyl]carbamoyl]pentyl]phosphinic acid;

N^2-[(R)-Hydroxycarbamoylmethyl]-4-methylvaleryl]-N^1,3-dimethyl-L-valinamide;

N^2-[2(R or S)-[[[(5-Bromo-2,3-dihydro-6-hydroxy)-1,3-dioxo-1H-benz[d,e]isoquinol-2-yl)methyl]-[(hydroxy)phosphinyl]methyl]-4-methylvaleryl]-N^1,3-dimethyl-L-valinamide;

N^2-[(R or S)-[[(R)-(Amino)[(5-bromo-2,3-dihydro-6-hydroxy-1,3-dioxo-1H-benz[d,e]isoquinol-2-yl)methyl](hydroxy)-phosphinyl]methyl]-4-methylvaleryl]-N^3,1-dimethyl-L-valinamide hydrobromide;

N^2-[2(R or S)-[1(S)-(Hydroxycarbamoyl)ethyl-4-methylvaleryl]-N^1,3-dimethylvalinamide;

N^2-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N^1,3-dimethyl-L-valinamide;

N^2-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-4-(methoxy-carbonyl)butyl]-4-methylvaleryl]-N^1,3-dimethyl-L-valinamide;

M^2-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-4-phenyl-butyl]-4-methylvaleryl]-N^1,3-dimethyl-L-valinamide;

N^2-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-succinimidoethyl]-4-methylvaleryl]-N^1,3-dimethyl-L-valinamide;

4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]morpholine;

4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine;

1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-4-piperidinol;

1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine;

4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine;

Hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N-methyl-3(S)-pyridazinecarboxamide;

1-[2(R)-(R or S)-(Hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol;

[4-(N-Hydroxyamino)-2(R or S)-heptylsuccinyl]-L-leucyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(R or S)-nonylsuccinyl]-L-leucyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(R or S)-heptyl-3(S)-methylsuccinyl]-L-leucyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(R)-heptyl-3(R or S)-(phthalimidomethyl)succinyl]-L-leucyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-nonylsuccinyl]-L-tert.butylglycine methylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-phenylalanine methylamide;

[4-(N-Hydroxyamino)-2(R)-heptyl-3(R or S)-phthalimidomethyl)succinyl]-L-tert.butylglycine methylamide;

[4-(N-Hydroxyamino)-2(R)-heptyl-3(R or S)-(3-phenylpropyl)-succinyl]-L-leucyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-leucine methylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-leucine neopentylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-alanyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-(N^{e}-phthaloyl)-lysyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-undecylsuccinyl]-L-leucyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-phenylalanyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-nonalyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-phenylalanine tert.butylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-tertbutylglycine methylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-neopentylglycine methylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-homophenylalanyl-L-leucine ethylamide;

[4-(N-Hydroxyamino)-2(RS)-heptylsuccinyl]-L-cyclohexylalanine methylamide;

[4-(N-Hydroxyamino)-2(RS)-isooctylsuccinyl]-L-phenylalanine methylamide;

[4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-L-neonpentylglycine methylamide;

[4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-(D or L)-β,β-dimethylphenylalanine methylamide;

[4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-(D or L)-threo-β-methylphenylalanine methylamide;

[4-(N-Hydroxyamino)-2(R)-heptylsuccinyl]-DL-erthro-β-methylphenylalanine methylamide;

[4-(N-Hydroxyamino)-2(R)-heptyl-3(R or S)-[(3-methyl-2,5-dioxo-1-imidazolidinyl)methyl]succinyl]-L-leucyl-L-leucine ethylamide;

N2-[3-Cyclobutyl-2(R or S)-[(hydroxycarbamoyl)-methyl]-propionyl]-N1,3-dimethyl-L-valinamide;

N2-[3-Cyclopropyl-2(R or S)-[(hydroxycarbamoyl)-methyl]-propionyl]-N1,3-dimethyl-L-valinamide;

N2-[3-Cyclopentyl-2(R or S)-[(hydroxycarbamoyl)-methyl]-propionyl]-N1,3-dimethyl-L-valinamide;

N2-[3-Cyclopropyl-2(R)-[1(R or S)-[(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-N1,3-dimethyl-L-valinamide;

N2-[3-Cyclopropyl-2(R)-[1(R or S)-[(hydroxy-carbamoyl)-4-phenylbutyl)]propionyl]-N1,3-dimethyl-L-valinamide;

N2-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-4-phenylbutyl]propionyl]-N1,3-dimethyl-L-valinamide;

N2-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]propionyl]-N1,3-dimethyl-L-valinamide;

1-[3-Cyclopropyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]piperidine;

1-[3-Cyclopropyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-4-piperidinol;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]piperidine;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-4-piperidinol;

1-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-4-piperidinol;

1-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]piperidine;

3-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-3-azabicyclo[3.2.2]nonane;

3-[3-Cyclopropyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-3-azabicyclo[3.2.2]nonane;

3-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-3-azabicyclo[3.2.2]nonane;

1-[3-Cyclohexyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]piperidine;

4-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]tetrahydro-1,4-thiazine;

4-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]tetrahydro-1,4-thiazine S,S-dioxide;

4-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]tetrahydro-1,4-thiazine;

3-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-5,5-dimethyl-N-propyl-[4(R)-thiazolidinecarboxamide;

4-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]morpholine;

3-[3-Cyclopentyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide;

4-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-4-phenylpiperazine;

4-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]morpholine;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxy-carbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]pyrrolidine;

8-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-1,4-dioxa-8-azaspiro[4,5]decane;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]-4-methoxypiperidine;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]octahydroazocine;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(5,5-dimethyl-2,4-dioxo-3-oxazolidinyl)ethyl]propionyl]piperidine;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]propionyl]hexahydroazepine;

1-[3-Cyclobutyl-2(R)-[2-(hexahydro-1,3-dioxo-pyrazolo[1,2-a][1,2,4]-triazol-2-yl)-1(R or S)-(hydroxycarbamoyl)ethyl]propionyl]piperidine;

1-[3-Cyclobutyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]propionyl]piperidine;

2-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-hexahydro-N-methyl-3(S)-pyridazinecarboxamide;

N-Cyclohexyl-hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide;

1-[2(R)-[1(R or S)-Hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-piperidine;

N2-[2(R)-[1(RS)-(Hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N1-methyl-L-prolinamide;

1-[2(R)-[l(R or S)-(Hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]piperidine;

Hexahydro-2-[2(R)-1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[(1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(1,2,2,6,6-pentamethyl-4-piperidinyl)-3(S)-pyridazine-carboxamide;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide;

1-[2(R or S)-[l(S)-(Hydroxycarbamoyl)ethyl]undecanoyl]piperidine;

1-[2-(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]piperidine;

Hexahydro-2-[2(R or S)-[l(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide;

Hexahydro-2-[2(R or S)-[l(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide;

1-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-piperidine;

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-morpholine;

1-(Benzyloxycarbonyl)-hexahydro-2-[2(R)-[(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(α(S)-methylbenzyl)-3(S)-pyridazinecarboxamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-5-(carboxy)pentanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(propylamino)-6-(oxo)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-(6RS)-6-(hydroxy)heptanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(hydroxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2′R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(4′-oxobutylamino)hexanoyl]-L-phenylalanine N-methylamide;

2(S)-N-2-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(oxo)-6′-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2R)-2-[(1′S)-1′-(Methyl)-2′-(hydroxyamino)-2′-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[(1′S)-1′-(Methyl)-2′-(hydroxyamino)-2′-(oxo)ethyl]-6-(oxo)-6-(propylamino)hexanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2[(2′R)-[(1"R)-1"-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl-2"-(hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(oxo)-6-(propylamino)hexanoyl]-L-phenylalanine N-2-phenylethylamide;

(2S)-N-2-[(2′R)-2′-[(1"S)-1"-(Methyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

(2S)-N-2-[(2′R)-2′-[(1"S)-1"-(Methyl)-2"-(hyroxyamino)-2"-(oxo)ethyl]-6′-(oxo)-6′-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

(2S)-N-2-[(2′R)-2′-[(1"S)-1"-(Methyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6′-(oxo)-6′-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4′-sulfamoyl)phenylethylamide;

(2S)-N-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4′-sulfamoyl)-phenylethylamide;

N-[2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6′-(phenyl-methoxy)hexanoyl]-L-(3,5-dimethyl)phenylalanine N-2-(4′-sulfamoyl)phenylethylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(4-methoxy)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4′-sulfamoyl)phenylethylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(4-methyl)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4′-sulfamoyl)phenylethylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(1-oxo)butylamino]hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4′-sulfamoyl)phenylethylamide;

(2S)-N-2-[(2′R)-2′-[(1"S)-1"-(Methyl)-2"-(hydroxyamino)--2"-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2-[(2′R)-2′-[(1"S)-1"-(2-Methylpropyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(phenoxy)-hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-7-(phenoxy)-heptanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4′-sulfamoyl)-phenylethylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-5-(phenylmethoxy)pentanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-7-(phenylmethoxy)heptanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(phenyloxy)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-7-[(phenyloxy)heptanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(2-phenethylamino)-6′-(oxo)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(4-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(4-chlorophenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(3-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-(carboxymethyl)-6′-(3-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-5-(carboxy)pentanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(propylamino)-6-(oxo)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-(6RS)-6-(hydroxy)heptanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(hydroxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2′R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(4′-oxobutylamino)hexanoyl]-L-phenylalanine N-methylamide;

2(S)-N-2-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(oxo)-4′-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2R)-2-[(1′S)-1′-(Methyl)-2′-(hydroxyamino)-2′-(oxo)ethyl]-6-phenylmethoxy)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[(l'S)-1'-(Methyl)-2'-(hydroxyamino)-2'-(oxo)ethyl]-6-(oxo)-(propylamino)hexanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2[(2'R)-[(1"R)-1"-(1,3-Dihydro-1,3-dioxo-2H-isoindol-yl)methyl-2"-(hydroxyamino)-2"-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6-(oxo)-6-(propylamino)hexanoyl]-L-phenylalanine N-2-phenylethylamide;

(2S)-N-2-[(2'R)-2'-[(1"S)-1"-(Methyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

(2S)-N-2-[(2'R)-2'-[(1"S)-1"-(Methyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6'-(oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

(2S)-N-2-[(2'R)-2'-[(1"S)-1"-(Methyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6'-(oxo)-6'-(propylamino)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;

(2S)-N-[(2'R)-2'-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4'-sulfamoyl)phenylethylamide;

N-[(2R)-2-[2'-(Hydroxyamino)-2'-(oxo)ethyl]-6'-(phenylmethoxy)hexanoyl]-L-(3,5-dimethyl)phenylalanine N-2-(4'-sulfamoyl)phenylethylamide;

(2S)-N-2'-[(2'R)-2'-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6`-[(4-methoxy)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)phenylethylamide;

(2S)-N-2'-[(2'R)-2'-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6'-[(4-methyl)phenoxy]hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4'-sulfamoyl)-phenylethylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(1-oxo)butylamino]hexanoyl]amino-3-cyclohexylpropionic acid N-2-(4′-sulfamoyl)-phenylethylamide;

(2S)-N-2-[(2′R)-2′-[(1"S)-1"-(Methyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2-[(2′R)-2′-[(1"S)-1"-(2-Methylpropyl)-2"-(hydroxyamino)-2"-(oxo)ethyl]-6-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(phenoxy)hexanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-7-(phenoxy)heptanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-phenylethylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-(phenylmethoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-2-(4′-sulfamoyl)phenylethylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-5-(phenylmethoxy)pentanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-7-(phenylmethoxy)heptanoyl]-L-phenylalanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-6-(phenyloxy)hexanoyl]-L-phenylelanine N-methylamide;

N-[(2R)-2-[2′-(Hydroxyamino)-2′-(oxo)ethyl]-7-[(phenyloxy)heptanoyl]-L-phenylalanine N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(2-phenethylamino)-6′-(oxo)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(4-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(4-chlorophenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-[2"-(Hydroxyamino)-2"-(oxo)ethyl]-6′-[(3-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(2S)-N-2′-[(2′R)-2′-(Carboxymethyl)-6′-(3-methylphenoxy)hexanoyl]amino-3,3-dimethylbutanoic acid N-methylamide;

(3*R*,10*S*)-5-Methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanoic acid;

(3*R*,10*S*)-*N*-Hydroxy-5-methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanamide;

(3*R*,11*S*)-*N*-Hydroxy-5-methyl-3-(10-oxo-1,9-diazatricyclo[11.6.1.0]eicosa-13(20),14(19),15,17-tetraen-11-ylcarbamoyl)hexanamide;

(3*R*,9*S*)-5-Methyl-3-(8-oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12(17),13,15-tetraen-9-ylcarbamoyl)hexanoic acid;

(3*R*,9*S*)-*N*-Hydroxy-5-methyl-3-(8-oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12(17),13,15-tetraen-9-ylcarbamoyl)hexanamide;

(10*S*)-[4-Methyl-2-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)pentyl]-(quinolin-2-ylthiomethyl)phosphinic acid;

(3*R*,10*S*)-*N*-Hydroxy-5-methyl-2-methoxycarbonyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanamide;

N-(4-Methyl-2-carboxymethylpentanoyl)-L-leucine-*N*′-(4-methoxycarbonylphenyl)carboxamide;

N-(4-Methyl-2-(*N*"-hydroxycarbamoyl)methylpentanoyl)-L-leucine-*N*′-(4-methoxycarbonylphenyl)carboxamide;

N-(4-Methyl-2-(*N*''-hydroxycarbamoyl)methylpentanoyl)-L-leucine-*N*'-(4-carboxyphenyl)carboxamide;

N-(4-Methyl-2-(*N*''-hydroxycarbamoyl)methylpentanoyl)-L-tryptophan-*N*'-(4-carboxyphenyl)carboxamide;

N-(4-Methyl-2-(*N*''-hydroxycarbamoyl)methylpentanoyl)-L-cyclohexylglycine-*N*'-(4-methoxycarbonylphenyl)carboxamide;

N-(4-Methyl-2-(*N*''-hydroxycarbamoyl)methylpentanoyl)-L-*t*-leucine-*N*'-(4-methoxycarbonylphenyl)carboxamide;

(3*R*,10*S*)-6-Biphenyl-4-yl)-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]onadeca-12(19),l3(18),14,l6-tetraen-10-ylcarbamoyl)hexanoic acid;

(3*R*,10*S*)-3-(9-Oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)-5-(thiophen-2-yl)pentanoic acid;

(3*R*,10*S*)-3-Cyclopentyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)propionic acid;

(3*R*,10*S*)-4-Cyclopentyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)butanoic acid;

(3*R*,10*S*)-4-Cyclopropyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-2(19),13(18),14,16-tetraen-10-ylcarbamoyl)butanoic acid;

(3*R*,10*S*)-5-Methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanoic acid;

(3*R*,10*S*)-*N*-Hydroxy-5-methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanamide;

(3*R*,11*S*)-*N*-Hydroxy-5-methyl-3-(10-oxo-1,9-diazatricyclo[11.6.1.0]eicosa-13(20),14(19),15,17-tetraen-11-ylcarbamoyl)hexanamide;

(3*R*,9S)-*N*-5-Methyl-3-(8-oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12(17),13,15-tetraen-9-ylcarbamoyl)hexanoic acid;

(3*R*,9*S*)-*N*-Hydroxy-5-methyl-3-(8-oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12(17),13,15-tetraen-9-ylcarbamoyl)hexanamide;

(10*S*)-2-Mercaptomethyl-4-methyl-*N*-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)pentanamide;

(10*S*)-2-Acetylthiomethyl-4-methyl-*N*-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)pentanamide;

(3*R*,10*S*)-2-(Methanesulfonamidomethyl)-5-methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanoic acid;

(3*R*,10*S*)-2-(3-Ethylureidomethyl)-5-methyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)hexanoic acid;

(3*R*,9*S*)-N-Hydroxy-2-hydroxy-5-methyl-3-(8-oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12(17),14,16-tetraen-9-ylcarbamoyl)hexanamide or its (2S,3R,9S) stereoisomer;

(3*R*,10*S*)-*N*-Hydroxy-5-methyl-2-methoxycarbonyl-3-(9-oxo-1,8-diazatricyclo[10.6.1.0]nonadeca-12(19),13(18),14,16-tetraen-10-ylcarbamoyl)-hexanamide;

(3R,9S)-5-Methyl-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-Cyclobutylmethyl-N-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)succinamic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-5-phenoxy-pentanoic acid;

(3R,9S)-5-(4-Chlorophenoxy)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid;

(3R,9S)-5-(4-Chlorophenoxy)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid ethyl ester;

(3R,9S)-3-(8-Oxo-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid ethyl ester;

(3R,9S)-6-(4-Hydroxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-pyridin-4-yl-hexanoic acid;

(3R,9S)-6-[4-(3-Hydroxy-propoxy)-phenyl]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-5-(4-phenoxy-phenyl)pentanoic acid;

(3R,9S)-6-[4-(2-Hydroxy-ethoxy)-phenyl]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-[4-(2-pyrrolidin-1-yl-ethoxyphenyl]hexanoic acid;

(3R,9S)-6-(4-Methoxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-6-[4-(2-Methoxy-ethoxy)-phenyl]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-5-phenyl-pentanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-phenyl-hexanoic acid;

(3R,9S)-6-(3-Hydroxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-[4-(3-piperidin-1-yl-propoxy)phenyl]hexanoic acid;

(3R,9S)-6-[4-(3-Dimethylamino-propoxy)-phenyl]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-6-[4-(2-Dimethylamino-ethoxy)-phenyl]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-6-(4-Cyano-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-6-Naphthalen-2-yl-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-(4-pyrrol-1-yl)hexanoic acid;

(3R,9S)-6-(4-Hydroxy-3-methyl-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-6-(4-Benzyloxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-6-[4-(4-Aminobutoxy-phenyl)]-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-5-(4-Methoxy-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)pentanoic acid;

(3R,9S)-6-(4-Amino-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]-octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

(3R,9S)-3-(8-Oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)-6-[4-(pyridin-4-ylmethoxy)phenyl]hexanoic acid;

(3R,9S)-6-(4-Acetylamino-phenyl)-3-(8-oxo-4-oxa-1,7-diazatricyclo[9.6.1.0]octadeca-11(18),12,14,16-tetraen-9-ylcarbamoyl)hexanoic acid;

N^{α}-[[3-(N-Hydroxycarbamoyl)-4-methylthio-2-propoxymethyl]butylyl]-N,O-dimethyltyrosine amide;

N^{α}-[[3-(N-Hydroxycarbamoyl)-4-isopropylthio-2-propoxymethyl]butylyl]-N,O-dimethyltyrosine amide;

N^{α}-[[3-(N-Hydroxycarbamoyl)-2-propylthio]butylyl]-N,O-dimethyltyrosine amide;

N-[N-(1-Phosphono-3-phenylpropyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

N-[N-(1-Phosphono-3-(4-bromo-1,8-naphthalene-dicarboximido)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide;

N-[N-(1-Phosphono-3-(benzyloxycarbonylamino)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide;

N-[N-(1-Phosphono-3-(2-hydroxyphenyl)propyl)-(S)-leucyl]-(S)-phenylalanine methylamide;

N-[N-(1-Phosphono-3-(methylmercapto)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

N-[N-(1-Phosphono-3-(methylsulphinyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

N-[N-(1-Phosphono-3-(methylsulphonyl)propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide;

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-tryptophan-N-methylamide;

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-methylamide;

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(-)-aminoazacyclotridecan-2-one;

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(aminoethyl)amide;

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethylpyrrolidine)amide;

N-[N-(1-Phosphono-3-(1,8-naphthalenedicarboximido)propyl)-(S)-leucyl]-(S)-lysine-N-(ethyl-N-methylpiperazine)amide;

N-[N-(1-Phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]propyl)-(S)-leucyl]-(S)-phenylalanine-N-methylamide; and

N-[N-(1-Phosphono-3-[8-(7,9-dioxo-8-azaspiro[4,5]decyl)]propyl)-(S)-leucyl]-(S)-lysine-N-methylamide.

As noted above, numerous inhibitors of matrix metalloproteinases are known. A large number of inhibitors are characterized as hydroxamic acid-based and/or carboxylic acid-based compounds. Typical of such compounds are those described in the following references, all of which are incorporated herein by reference since all of the disclosed compounds can be used in the method of this invention.

US 4599361	(Searle)
EP-A-2321081	(ICI)
EP-A-0236872	(Roche)
EP-A-0274453	(Bellon)
WO 90/05716	(British Biotechnology)
WO 90/05719	(British Biotechnology)
WO 91/02716	(British Biotechnology)
WO 92/09563	(Glycomed)
US 5183900	(Glycomed)
US 5270326	(Glycomed)
WO 92/17460	(Smith-Kline Beecham)
EP-A-0489577	(Celltech)
EP-A-0489579	(Celltech)
EP-A-0497192	(Roche)
US 5256657	(Sterling Winthrop)
WO 92/13831	(British Biotechnology)
WO 92/22523	(Research Corporation Technologies)
WO 93/09090	(Yamanouchi)
WO 93/09097	(Sankyo)

WO 93/20047	(British Biotechnology)
WO 93/24449	(Celltech)
WO 93/24475	(Celltech)
EP-A-0574758	(Roche)
WO 94/02447	(British Biotechnology)
WO 94/02446	(British Biotechnology)

An especially preferred group of compounds to be employed in the present method are those described in WO 95/35275 and WO 95/35276, both of which are incorporated herein by reference. Typical compounds from within these groups to be employed include:

N-Hydroxy-2-[[(2-(4-methoxy-phenoxy)-ethyl-(toluene-4-sulfonyl)-amino]-acetamide;

N-Hydroxy-2-[(4-phenoxy-ethyl)-toluene-4-sulfonyl) amino]-acetamide;

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-nonyl-amino]-acetamide;

2-[-Decyl-(toluene-4-sulfonyl)-amino]-N-hydroxy-acetamide;

2-Benzyl-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;

N-Hydroxy-2-[(2-methoxy-benzyl)-(octane-1-sulfonyl)-amino]-acetamide;

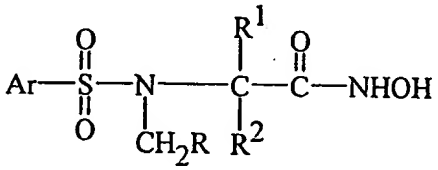
2-[(2-Ethoxy-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;

N-Hydroxy-2-[(naphthalen-2-yl-methyl)-(octane-1-sulfonyl)-amino]-acetamide;

2-[(4-Chloro-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide,

and salts, solvates, or hydrates thereof.

Another class of matrix metalloproteinase inhibitors are aryl sulfonamides of the formula



where Ar is carbocyclic or heterocyclic aryl, and R, R^1, and R^2 include hydrogen, alkyl, aryl, heteroaryl, amino, substituted and disubstituted amino. These compounds are disclosed in European Patent Number 0606046, incorporated

herein by reference. Specific compounds to be employed in the present method include:

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl) amino]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclo-hexylmethyl)amino]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclo-hexyl)amino]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](phenethyl) amino]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-methylbutyl)amino]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](sec-butyl)amino]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](tert-butyl)amino]acetamide

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-fluorobenzyl)amino]acetamide

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-chlorobenzyl)amino]acetamide

N-Hydroxy-2-[[4-methoxybenzenesulfonyl] (isopropyl)-amino]acetamide

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-methylbenzyl)amino]acetamide

4-N-Hydroxy-carbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[dimethylaminoacetyl]-piperidine hydrochloride

4-N-Hydroxy-carbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[3-picolyl]-piperidine dihydrochloride

4-N-Hydroxy-carbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[carbomethoxymethyl]-piperidine hydrochloride

4-N-Hydroxy-carbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-piperidine trifluoroacetate;

4-N-Hydroxy-carbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[t-butoxycarbonyl]-piperidine;

4-N-Hydroxycarbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[methylsulfonyl]-piperidine;

N-Hydroxycarbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)-amino]-1-[4-picoly]-piperidine hydrochloride;

N-Hydroxycarbamoyl]-4-[[4-methoxybenzene-sulfonyl(benzyl)amino]-1-[morpholinocarbonyl]-piperidine hydrochloride; and

N-(t-Butyloxy)-2-[[4-methoxybenzenesulfonyl (benzyl)amino]-2-[2-(4-morpholino)ethyl]acetamide.

The following compounds are prepared similarly to Example 7:

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)- amino-2-(2-(4-morpholino)ethyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picoly)- amino-2-(2-(4-morpholino)ethyl]acetamide dihydro-chloride;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl] (3-picolyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methyl-thiazol-4-ylmethyl)amino]-2-[2-(4-morpholino) ethyl]acetamide dihydrochloride;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl] benzyl)amino]-2-[2-(4-thiomorpholino]ethyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl] (benzyl)amino]-2-[2-(4-methylthiazol-4-ylmethyl] acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl (benzyl)amino]-2-[(6-chloropiperonyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl (benzyl)amino]-2-[(1-pyrazolyl)methyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl (3-picolyl)amino]-2-[3-picolyl]acetamide;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl(benzyl)-amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride;

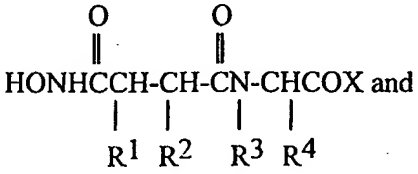
N-Hydroxy-2-[[4-methoxybenzenesulfonyl(isobutyl) amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride;

N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl) amino]-2-[(1-methyl-4-imidazolyl) methyl]acetamide hydrochloride;

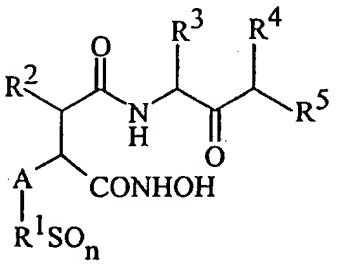
N-Hydroxy-2-[[4-methoxybenzenesulfonyl(2-picolyl) amino]-2-[(1-methyl-4-imidazolyl)methyl]-acetamide hydrochloride; and

N-Hydroxy-2-[[4-methoxybenzenesulfonyl] (2-methylthiazol-4-ylmethyl)amino-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride.

Another group of small peptide matrix metalloproteinase inhibitors are described in United States Patent Numbers 5,270,326, 5,530,161, 5,525,629, and 5,304,604 (incorporated herein by reference). The compounds are hydroxamic acids defined by the formula.



and



where R^1, R^2, R^3, and R^4 can be hydrogen or alkyl and X is OR^5 or NHR^5 where R^5 includes hydrogen, alkyl and aryl, A includes alkyl, and n is 0 to 2. Typical compounds to be employed in the instant method include the following:

N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-D-tryptophan methylamide;

N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-N-methyl-L-tryptophan methylamide;

N-[2-Isobutyl-3-(N-hydroxycarbonylamido)-propanoyl]-L-3-(2-naphthyl)-alanine methylamide;

N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-L-tryptophan 2-hydroxyethylamide;

N-[2-Isobutyl-3-(N'-hydroxycarbonylamido)-propanoyl]-L-tryptophan amylamide;

N-[2-Isobutyl-3-(N′-hydroxycarbonylamido)-propanoyl]-L-tryptophan piperidinamide;

N-[2-Isobutyl-3-(N′-hydroxycarbonylamido)-propanoyl-L-tryptophan dodecylamide;

N-[2-Isobutyl-3-(N′-hydroxycarbonylamido)-propanoyl]-L-tryptophan(S)-methylbenzylamide;

N-[L-2-Isobutyl-3-(N′-hydroxycarbonylamido)-propanoyl]-L-tryptophan(6-phenylmethoxycarbonyl-amino-hexyl-1)amide;

2S-Hydroxy-3R-[1S-(3-methoxy-2,2-dimethyl-propylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-6-(4-chloro)phenyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propyl-carbamoyl]octanohydroxamic acid;

2S-Hydroxy-3R-[1S-(pyridin-2-ylmethylcarbamoyl)-2,2-dimethyl-propyl-carbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(pyridin-3-ylmethylcarbamoyl)-2,2-dimethyl-propyl-carbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(pyridin-4-ylmethylcarbamoyl)-2,2-dimethyl-propyl-carbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-methoxy-butanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-benzyloxy-butanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-benzylthio-butanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-buten-3-ylcarbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(*tert*-butylcarbamoyl)-2,2-dimethyl-propyl-carbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(N,N-dimethyl-carbamoyl)-2,2-dimethyl-propyl-carbamoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(3-hydroxy-2,2-dimethyl-propylcarbamoyl)-2,2-dimethyl-propylcarbanoyl]-5-methyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-6-phenyl-hexanohydroxamic acid;

2S-Hydroxy-3R-[1S-(methylcarbamoyl)-2,2-dimethyl-butylcarbamoyl]-5-methyl-hexanohydroxamic acid;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(2-hydroxyethyl)-amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalaninyl-proline;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(2-hydroxyethyl)-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalaninyl-D-prolinol;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalaninyl-L-prolinol;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(5-N-methyl-pentylcarboxamide)amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(2-ethylthioethyl)amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(2-methoxyethyl)amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(2-N-acetylethyl)amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide sodium salt;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(2-acetoxyethyl)amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-methyl-N-(2-hydroxyethyl)amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(2-hydroxyethyl)amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalaninyl-D-prolinol;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide sodium salt;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide or a salt thereof;

N^2-[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]-N^6-*tert*-butyloxycarbonyl-L-lysine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]-N^6-*tert*-butyloxycarbonyl-N^6-(4-hydroxyphenylthiomethyl)-L-lysine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-3S-(2-thienylthiomethyl)-2R-isobutylsuccinyl]-N^6-*tert*-butyloxycarbonyl-L-lysine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]-O-*tert*-butyl-L-threonine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylthiomethyl)-2R-isobutylsuccinyl]-L-glutamine-N^1,N^5-dimethylamide;

N^2-[4-(N-Hydroxyamino)-3S-(4-hydroxyphenylsulphonylmethyl)-2R-isobutylsuccinyl]-N^6-acetyl-L-lysine-N^1-methylamide;

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

3R-(1S-Methylcarbamoyl-2-thien-2-yl-ethylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

3R-(3-Methyl-1S-methylcarbamoyl-butylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

2S-[1S-Methylcarbamoyl-2-oxadiazol-5-yl-ethylcarbamoyl)-5-methyl-2S-2-propenyl-hexanohydroxamic acid;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxylic acid)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-methylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-beta-alanine)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxyglycine)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-benzylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-cyano)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-acetamido)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-henylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethylsuccinyl]-L-(4-N-acetylamino)-henylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethylsuccinyl]-L-(4-N-methylsuccinylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(methylsuccinylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethylsuccinyl]-L-(4-N-(4-(4-oxobutanoic acid)aminophenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-methylsuccinylamido)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)aminophenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-oxymethylcarboxymethyl)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(oxymethylcarboxylic acid)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-oxymethylcarboxyglycine)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-4-oxymethylnitrile)-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-(2-methyloxycarbonyl)-ethyl)-4-methoxyphenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-3-(hydroxymethyl)-4-methoxyphenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-3-methyl-4-methoxyphenylalanine-N-methylamide;

2-[Benzyl-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;

N-Hydroxy-2-[(2-methoxy-benzyl)-(octane-1-sulfonyl)-amino]-acetamide;

2-[(2-Ethoxy-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;

N-Hydroxy-2-[(naphthalen-2-yl-methyl)-(octane-1-sulfonyl)-amino]-acetamide;

2-[(4-Chloro-benzyl)-(octane-1-sulfonyl)-amino]-N-hydroxy-acetamide;

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-leucine-N^1-methylamide;

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl)]-5-methyl-L-glutamic acid-N^1-methylamide;

N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl)]-L-phenylalanine-N^1-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thienylthiomethyl)succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide;

2S-(4-Methoxyphenylsulfanylmethyl)-3R-(2-phenyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(3-Chlorophenylsulfanylmethyl)-3R-(2-phenyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Phenylsulfanylmethyl)-3R-(2-phenyl-1S-(pyrid-3-ylmethylcarbamoyl)-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(3-Methylphenylsulfanylmethyl)-3R-(2-phenyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Thien-2-ylsulfanylmethyl)-3R-(2-(4-carboxymethoxyphenyl)-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Thien-2-ylsulfanylmethyl)-3R-(2-phenyl-1S-(pyrid-3-ylmethylcarbamoyl)-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2-phenyl-1S-(pyrid-3-ylmethylcarbamoyl)-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Thien-2-ylsulfanylmethyl)-3R-(2-naph-2-yl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(2R-hydroxy-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(5-acetamido-1S-methylcarbamoyl-pentylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxyphenylsulfanylmethyl)-3R-(3-[1,1-dimethylethoxycarbonyl]-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Thien-2-ylsulfonylmethyl)-3R-(2-phenyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

3S-(2-[4-Acetamido-phenyl]-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Phthalimido-butyl)-3R-(3-methyl-1S-ethoxycarbonylmethylcarbamoyl-butylcarbamoyl)-5-methyl-hexanohydroxamic acid;

3R-(2-[4-Methoxy-phenyl]-1S-methylcarbamoyl-ethylcarbamoyl)-2S,5-dimethyl-hexanohydroxamic acid;

3R-(2-Phenyl-1S-[2-oxo-pyrolid-1-yl]-propylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

3R-(2-[4-Methoxy-phenyl]-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

3R-(2-Phenyl-1S-[pyrid-3-ylmethylcarbamoyl]-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

3R-(2,2-Dimethyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

Isobutylmalonoyl-L-alanine-furfurylamide hydroxamate;

2-Isobutyl-3-carbonyl-3′-(4-acetylaniline)propionic acid;

N-Benzyloxycarbonyl-α-phosphonoglycyl-L-alanine furfurylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-dimethylphenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methylphenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-amino-phenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphinylmethylsuccinyl]-L-phenylalanine-N-methylamide;

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-phenylsulfanylmethyl- hexanohydroxamic acid;

3R-(3-Methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-2S-(thien-2-ylsulfanylmethyl)-hexanohydroxamic acid;

2S-(4-Methoxy-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Amino-phenylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Ethylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Acetylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(Benzylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(*tert*-Butylsulfanylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-Thiomethyl-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxy-phenylsulfanylmethyl)-3R-(2-*tert*-butoxycarbonyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxy-phenylsulphinylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

2S-(4-Hydroxy-phenylsulphonylmethyl)-3R-(3-methoxycarbonyl-1S-methylcarbamoyl-propylcarbamoyl)-5-methyl-hexanohydroxamic acid;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-[1-(2-aminoethyl)-pyrrolidine]amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-[1-(3-aminopropyl)-2(RS)-methylpiperidine]amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-[2-(2-aminoethyl)-1-methylpyrrole]amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(3-aminomethylpyridine)amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(2-aminomethylpyridine)amide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenylalanine-N-(4-aminomethylpyridine)amide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenylalanine-N-(1-(3-aminopropyl)-imidazole)amide;

[4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenylalanine-N-(2-aminomethylbenzimdazole)amide;

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholino]amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide;

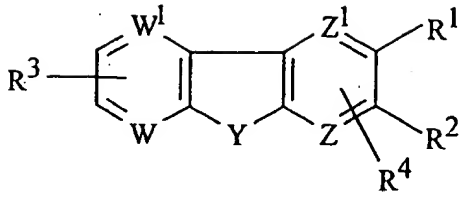
[4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide;

[4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenylalanine-N-[4-(2-aminopropyl)-morpholine]amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(3-aminomethylpyridine)amide hydrochloride; and

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide hydrochloride.

In a preferred embodiment, tricyclic butyric acid derivatives which are inhibitors of matrix metalloprotienases are employed to treat neurological disorder and to promote wound healing according to this invention. A preferred group of tricyclic butyric acid derivatives are defined by the formula:



wherein one of R^1 or R^2 is -C(=O)-CH(R)-$(CH)_a$-C(=X)-R^5 (R = R^a)

wherein X is O,

N-OR^6 wherein R^6 is hydrogen,

-$(CH_2)_n$-aryl wherein n is zero or an integer of 1 to 5, alkyl, or

-$(CH_2)_n$-cycloalkyl wherein n is as defined above, or

N-N-R^6 wherein R^6 and R^{6a} are each the same or different and each (R^{6a})

is as defined above for R^6;

R and R^a are each the same or different and each is hydrogen,

-$(CH_2)_n$-aryl wherein n is as defined above,

-$(CH_2)_n$-heteroaryl wherein n is as defined above,

-$(CH_2)_p$-R^7-$(CH_2)_q$-aryl wherein R^7 is O or S and p or q is each zero or an integer of 1 to 5 and the sum of p + q equals an integer of 5,

-$(CH_2)_p$-R^7-$(CH_2)_q$-heteroaryl

wherein p, q, and R^7 are as defined above,

alkyl,

-$(CH_2)_n$-cycloalkyl wherein n is as defined above, or

-$(CH_2)_r$-NH_2 wherein r is an integer of 1 to 9;

a is zero or an integer of 1 to 3;

R^5 is OH,

OR^6 wherein R^6 is as defined above,

NR^6 wherein R^6 and R^{6a} are each the same or different and are as defined above for R^6, or $NH\text{-}OR^6$ wherein R^6 is as defined above;

R^3 and R^4 are each the same or different and each is hydrogen,

alkyl,

NO_2,

halogen,

OR^6 wherein R^6 is as defined above,

CN,

CO_2R^6 wherein R^6 is as defined above,

SO_3R^6 wherein R^6 is as defined above,

CHO,

$-C(=O)-R$ wherein R is as defined above,

$-C(=O)-N(R^6)-R^{6a}$ wherein R^6 and R^{6a} are each the same or different and are as defined above for R^6, or

$-(CH_2)_n-N(R^6)-R^{6a}$ wherein R^6 and R^{6a} are each the same or different and are as defined above for R^6;

W, W^1, Z, and Z^1 are each the same or different and each is CR^3 wherein R^3 is as defined above, or

N providing only one of W or W^1 is N and/or only one of Z or Z^1 is N; and

Y is -N- wherein R is as defined above,
|
R

-O-,

-S-(O)$_m$- wherein m is zero or an integer of 1 or 2,

-CH_2-,

-C-,
‖
O

-C- wherein R^6 is as defined above,
|
N-OR^6

-CH- wherein R^6 is as defined above,
|
OR^6

-C- wherein R^6 and R^{6a} are the same or
‖
N-N-R^6 different and are as defined
|
R^{6a} above for R^6,

-C-N- wherein R^6 is as defined above,
‖ |
O R^6

-N-C- wherein R^6 is as defined above,
‖ |
R^6O

-C-O-,
|
O

-O-C-,
|
O

-CH_2-O-,

-O-CH_2-,

-CH_2-S(O)$_m$- wherein m is as defined above,

-S(O)$_m$-CH_2- wherein m is as defined above,

$-CH_2-N-$ wherein R^6 is as defined above,

$-N-CH_2-$ wherein R^6 is as defined above,

-CH=N-, or

-N=CH-;

with the proviso that when X is O, and R^5 is not $NH-OR^6$, at least one of R or R^a is not hydrogen; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

Typical compounds from this class include:

4-Dibenzofuran-2-yl-4-hydroxyimino-butyric acid; 2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-4-methyl-pentanoic acid;

2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-phenyl-pentanoic acid;

4-Dibenzofuran-2-yl-4-hydroxyimino-2-phenethyl-butyric acid;

5-(4-Chloro-phenyl)-2-(2-dibenzofuran-2-yl-2-hydroxyimino-ethyl)-pentanoic acid;

2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-(4-fluoro-phenyl)-pentanoic acid;

2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-(4-methoxy-phenyl)-pentanoic acid;

2-(2-Dibenzofuran-2-yl-2-hydroxyimino-ethyl)-5-p-tolyl-pentanoic acid;

3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-5-methyl-hexanoic acid;

3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-phenyl-hexanoic acid;

3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-5-phenyl-pentanoic acid;

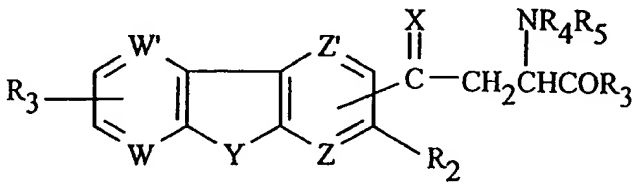
6-(4-Chloro-phenyl)-3-(dibenzofuran-2-yl-hydroxyimino-methyl)-hexanoic acid;

3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-(4-fluoro-phenyl)-hexanoic acid;

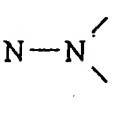
3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-(4-methoxyphenyl)-hexanoic acid; and

3-(Dibenzofuran-2-yl-hydroxyimino-methyl)-6-p-tolyl-hexanoic acid; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

Tricyclic butyric acids having an α-amino substituent are defined by the formula:



wherein:

X is O, NOR_9, S, OH, SH, or  ;

R_7 and R_{7a} independently are

hydrogen,

C_1-C_{20} alkyl or substituted C_1-C_{20} alkyl,

$(CH_2)_{0-6}$-aryl,

$(CH_2)_{0-6}$-heteroaryl, or

$(CH_2)_{0-6}$-cycloalkyl;

R_1 and R_2 independently are

hydrogen,

C_1-C_{20} alkyl or substituted C_1-C_{20} alkyl,

halo,

NO_2,

CN,

CHO,

COR_6,

$COOR_6$,

SO_3R_6,

OR_6,

$CONR_4R_5$,

$(CH_2)_{0-6}$-aryl,

$(CH_2)_{0-6}$-heteroaryl, or

$(CH_2)_{0-6}$-cycloalkyl;

R_6 is hydrogen,

C_1-C_{20} alkyl or substituted C_1-C_{20} alkyl;

aryl is phenyl or substituted phenyl;

R_3 is hydroxy,

O-C_1-C_{20} alkyl or substituted O-C_1-C_{20} alkyl,

O-$(CH_2)_{1-3}$ aryl, or

$NHOR_6$;

R_4 and R_5 independently are hydrogen,

C_1-C_{20} alkyl or substituted C_1-C_{20} alkyl,

$(CH_2)_{0-6}$-aryl,

$(CH_2)_{0-6}$-heteroaryl; or one of R_4 and R_5 is hydrogen and the other is:

COR_8,

CSR_8,

$CONR_8R_9$,

$CSNR_8R_9$,

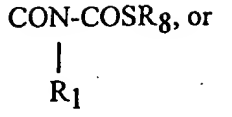
$COOR_8$,

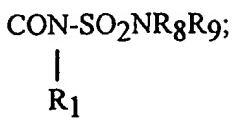
$COSR_8$,

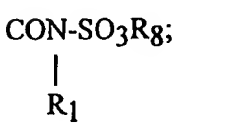
$COCHR_8$,
|
NR_1R_2,

CON-$CONR_8R_9$,
|
R_1

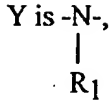
CON-$COOR_8$,
|
R_1







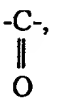
Y is

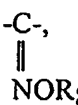


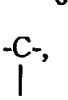
-O-,

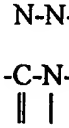
-S(O)0, 1, or 2,

-CH2-,









-CH2-O-,

-O-CH_2-,

-$CH_2S(O)_{0, 1, or 2}$,

-$S(O)_{0, 1, or 2}$ -CH_2-,

-CH_2-N-,
|
R_8

-N-CH_2-,
|
R_8

-CH=N, or

-N=CH-;

R_8 and R_9 independently are

hydrogen

C_1-C_{20} alkyl or substituted C_1-C_{20} alkyl,

$(CH_2)_{0-6}$-aryl,

$(CH2)_{0-6}$-heteroaryl, or

$(CH_2)_{0-6}$-cycloalkyl;

W, W′, Z, and Z′ independently are CR_1 or N;

and the pharmaceutically acceptable salts, isomers, stereoisomers, and solvates thereof.

Specific examples of compounds to be employed in the present method include:

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetylamino)-butyric acid;

(R)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetylamino)-butyric acid;

(S)-2-Amino-4-dibenzofuran-2-yl-4-oxo-butyric acid

(S)-2-Acetylamino-4-dibenzofuran-2-yl-4-oxo-butyric;

(S)-4-Dibenzofuran-2-yl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-4-oxo-butyric acid;

(S)-2-Benzoylamino-4-dibenzofuran-2-yl-4-oxo-butyric acid

(S)-4-Dibenzofuran-2-yl-4-oxo-2-phenylacetylamino-butyric acid;

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(3-phenyl-propionylamino)-butyric acid;

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(7-phenyl-heptanoylamino)-butyric acid;

(S)-2-[(Biphenyl-4-carbonyl)-amino]-4-dibenzofuran-2-yl-4-oxo-butyric acid;

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(dodecanoylamino)-butyric acid;

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(dodecanoyl-amino)-butyric acid;

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetylamino)-butyric acid;

(R)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetylamino)-butyric acid;

(S)-2-Amino-4-dibenzofuran-2-yl-4-oxo-butyric acid;

(S)-2-Acetylamino-4-dibenzofuran-2-yl-4-oxo-butyric acid;

(S)-4-Dibenzofuran-2-yl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-4-oxo-butyric acid;

(S)-2-Benzoylamino-4-dibenzofuran-2-yl-4-oxo-butyric acid;

(S)-4-Dibenzofuran-2-yl-4-oxo-2-phenylacetylamino-butyric acid;

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(3-phenyl-propionylamino)-butyric acid;

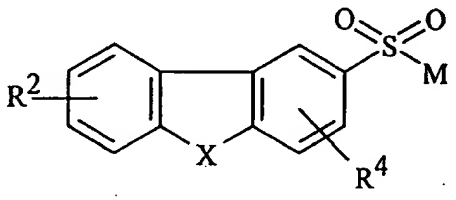
(S)-4-Dibenzofuran-2-yl-4-oxo-2-(7-phenyl-heptanoylamino)-butyric acid;

(S)-2-[(Biphenyl-4-carbonyl)-amino]-4-dibenzofuran-2-yl-4-oxo-butyric acid;

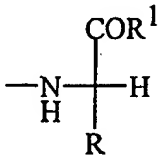
(S)-4-Dibenzofuran-2-yl-4-oxo-2-(octanoylamino)-butyric acid; and

(S)-4-Dibenzofuran-2-yl-4-oxo-2-(dodecanoylamino)-butyric acid.

Tricyclic sulfonamide matrix metalloproteinase inhibitors include compounds of the formula



wherein M is a natural (L) alpha amino acid derivative having the structure



X is O, S, $S(O)_n$, CH_2, CO, or NH;

R is a side chain of a natural alpha amino acid;

R^1 is C_1-C_5 alkoxy, hydroxy, or -$NHOR^5$;

R^2 and R^4 are independently hydrogen, -C_1-C_5 alkyl, -NO_2, halogen, -OR^5, -CN, -CO_2R^5, -SO_3R^5,-CHO, -COR^5, -$CONR^5R^6$, -$(CH_2)_nNR^5R^6$, -CF_3, or -$NHCOR^5$;

each R^5 and R^6 are independently hydrogen or C_1-C_5 alkyl; and

n is 0 to 2, and the pharmaceutically acceptable salts, ester, amides, and prodrugs thereof.

Specific compounds from this class to be employed include:

(L)-2-(Dibenzofuran-2-sulfonylamino)-4-methyl-pentanoic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-pentanoic acid

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-phenyl-propionic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-propionic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid;

(Dibenzofuran-2-sulfonylamino)-acetic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-succinic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-tritylsulfanyl-propionic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-mercapto-propionic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-pentanoic acid hydroxyamide;

(L)-2-(Dibenzofuran-2-sulfonylamino)-4-methyl-pentanoic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-pentanoic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-phenyl-propionic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-propionic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid;

(Dibenzofuran-2-sulfonylamino)-acetic acid;

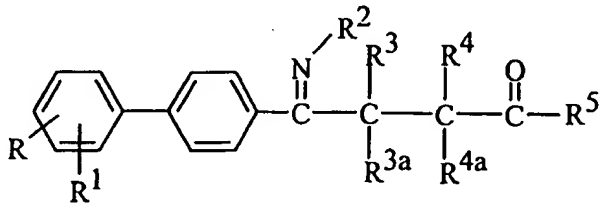
(L)-2-(Dibenzofuran-2-sulfonylamino)-succinic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-tritylsulfanyl-propionic acid;

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-mercapto-propionic acid; and

(L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-pentanoic acid hydroxyamide.

Additional MMP inhibitors are defined by the formula:



wherein R and R^1 are the same or different and are

hydrogen,

alkyl,

halogen,

nitro,

cyano,

trifluoromethyl,

$-OR^6$ wherein R^6 is hydrogen,

alkyl,

aryl,

arylalkyl,

heteroaryl, or

cycloalkyl,

$-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are

as defined above for R^6, $-O-C(=O)-R^6$ wherein R^6 is as defined above,

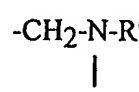
$-NH-C(=O)-R^6$ wherein R^6 is as defined above,

$-S-C(=O)-R^6$ wherein R^6 is as defined above,

$-SR^6$ wherein R^6 is as defined above,

-C-R^6 wherein R^6 is as defined above,

-CH_2-OR^6 wherein R^6 is as defined above,



-CH_2-N-R^6 wherein R^6 and R^{6a} are the same or

different and are as defined above for R^6,

-C-N-R^6 wherein R^6 and R^{6a} are the same or

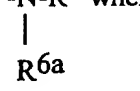
different and are as defined above for R^6,

-S-R^6 wherein R^6 is as defined above,

cycloalkyl, or

heteroaryl, with the proviso that R and R^1 are not both hydrogen;

R^2 is -OR^6 wherein R^6 is as defined above, or



-N-R^6 wherein R^6 and R^{6a} are the same or

different and are as defined above for R^6;

R^3, R^{3a}, R^4, and R^{4a} are the same or different and are

hydrogen,

fluorine,

alkyl,

-$(CH_2)_n$-aryl wherein n is an integer from 1 to 6,

-$(CH_2)_n$-heteroaryl wherein n is as defined above,

-$(CH_2)_n$-cycloalkyl wherein n is as defined above,

$-(CH_2)_p-X-(CH_2)_q$-aryl wherein X is O, S, SO, SO_2, or NH, and p and q are each zero or an integer of 1 to 6, and the sum of p + q is not greater than six,

$-(CH_2)_p-X-(CH_2)_q$-heteroaryl wherein X, p, and q are as defined above, or

$-(CH_2)_n-R^7$ wherein R^7 is

N-phthalimido,

N-2,3-naphthyimido,

$-OR^6$ wherein R^6 is as defined above,

$-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-SR^6$ where R^6 is as defined above,

$-S(=O)-R^6$ wherein R^6 is as defined above,

$-S(=O)_2-R^6$ wherein R^6 is as defined above,

$-O-C(=O)-R^6$ wherein R^6 is as defined above,

$-N(R^{6a})-C(=O)-R^6$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-S-C(=O)-R^6$ wherein R^6 is as defined above,

$-C(=O)-R^6$ wherein R^6 is as defined above,


-C-OR^6 wherein R^6 is as defined above, or


-C-N-R^6 wherein R^6 and R^{6a} are the same


or different and are as defined above for R^6, and

n is as defined above;

R^5 is OH or SH; with the proviso that R^3, R^{3a}, R^4, and R^{4a} are hydrogen or at least one of R^3, R^{3a}, R^4, or R^{4a} is fluorine; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

Typical compounds from this class that are routinely utilized in the present method include:

4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(4′-Bromo-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-4-(dimethylhydrazono)- butyric acid;

4-(4′-Fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxy-butyric acid;

4-(4′-Bromo-2′-fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-3-fluoro-4-oxo-butyric acid;

4-(2′,4′-Dichloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(2′,4′-Difluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(3-phenylpropyl)-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(2-phenylethyl)-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(3-phthalimidopropyl)-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(phenylthiomethyl)-butyric acid;

4-(4′-Chloro-2′-fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-Hydroxyimino-4-(4′-trifluoromethyl-biphenyl-4-yl)-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-4-methoxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-2-fluoro-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(1H-indol-3-yl)methyl-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-methyl-butyric acid;

(±)-2-[2-(4′-Chloro-biphenyl-4-yl)-2-hydroxyiminoethyl]-2-fluoro-6-phenyl-hexanoic acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-2-fluoro-2-[2-(1,3-dioxo-1,3-dihydro-benzo[F]isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

(±)-2-[2-(4′-Chloro-biphenyl-4-yl)-2-hydroxyiminoethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-fluoro-hexanoic acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-[2-(phenyl-ethylcarbamoyl)-ethyl]-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-3,3-difluoro-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-3,3-dimethyl-2-fluoro-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-2,2-dimethyl-3-fluoro-4-hydroxyimino-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-2,2-difluoro-4-hydroxyimino-butyric acid; and

4-(4′-Chloro-biphenyl-4-yl)-2,2,3,3-tetrafluoro-4-hydroxyimino-butyric acid.

A compound selected from the group consisting of:

4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(4′-Bromo-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-4-(dimethylhydrazono)- butyric acid;

4-(4′-Fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxy-butyric acid;

4-(4′-Bromo-2′-fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-3-fluoro-4-oxo-butyric acid;

4-(2′,4′-Dichloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-(2′,4′-Difluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(3-phenylpropyl)-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(2-phenylethyl)-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(3-phthalimidopropyl)-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(phenylthiomethyl)-butyric acid;

4-(4′-Chloro-2′-fluoro-biphenyl-4-yl)-4-hydroxyimino-butyric acid;

4-Hydroxyimino-4-(4′-trifluoromethyl-biphenyl-4-yl)-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-4-methoxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-2-fluoro-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-(1H-indol-3-yl)methyl-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-methyl-butyric acid;

(±)-2-[2-(4′-Chloro-biphenyl-4-yl)-2-hydroxyiminoethyl]-2-fluoro-6-phenyl-hexanoic acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-2-fluoro-2-[2-(1,3-dioxo-1,3-dihydro-benzo[F]isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

(±)-2-[2-(4′-Chloro-biphenyl-4-yl)-2-hydroxyiminoethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-fluoro-hexanoic acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-4-hydroxyimino-2-fluoro-2-[2-(phenyl-ethylcarbamoyl)-ethyl]-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-3,3-difluoro-4-hydroxyimino-butyric acid;

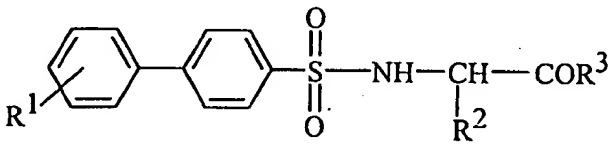
(±)-4-(4′-Chloro-biphenyl-4-yl)-3,3-dimethyl-2-fluoro-4-hydroxyimino-butyric acid;

(±)-4-(4′-Chloro-biphenyl-4-yl)-2,2-dimethyl-3-fluoro-4-hydroxyimino-butyric acid;

4-(4′-Chloro-biphenyl-4-yl)-2,2-difluoro-4-hydroxyimino-butyric acid; and

4-(4′-Chloro-biphenyl-4-yl)-2,2,3,3-tetrafluoro-4-hydroxyimino-butyric acid.

Biphenyl sulfonamides are also particularly good in the present method. Such compounds include those of the formula:



wherein:

R^1 is C_1-C_6 alkyl, halo, nitro, NR^4R^5, cyano, OR^4, and $COOR^4$;

R^2 is C_1-C_6 alkyl, optionally substituted by phenyl, substituted phenyl, NR^4R^5, OR^6,

carboxy, carboxamido, H_2N-C-NH-, thio, methylthio, indole, imidazole, phthalimido, phenyl, and substituted phenyl;

R^3 is OH, OC_1-C_6 alkyl, or NHOH;

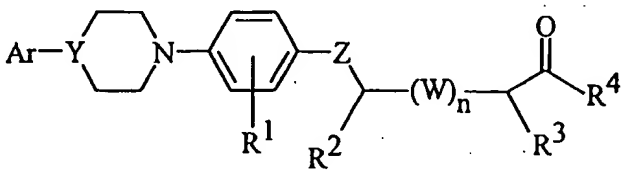
R^4 is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkanoyl;

R^5 is hydrogen or C_1-C_6 alkyl; and

R^6 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl, or substituted phenyl.

Specific compounds which can be employed include a compound of the above formula wherein R^1 is at the 4′ position.

Another class of matrix metalloproteinase inhibitors useful in the present method are the heterocyclic substituted phenyl butyric acid derivatives, for example those defined by the formula:



Ar is selected from phenyl,

phenyl substituted with

alkyl,

NO_2,

halogen,

OR^5 wherein R^5 is hydrogen or alkyl,

CN,

CO_2R^5 wherein R^5 is as defined above,

SO_3R^5 wherein R^5 is as defined above,

CHO,

COR^5 wherein R^5 is as defined above,

$CONHR^5$ wherein R^5 is as defined above, or

$NHCOR^5$ wherein R^5 is as defined above,

2-naphthyl, or

heteroaryl;

R^1 is selected from hydrogen,

methyl,

ethyl,

NO_2,

halogen,

OR^5 wherein R^5 is as defined above,

CN,

CO_2R^5 wherein R^5 is as defined above,

SO_3R^5 wherein R^5 is as defined above,

CHO, or

COR^5 wherein R^5 is as defined above;

R^2 and R^3 are the same or different and independently selected from hydrogen,

alkyl,

$-(CH_2)_v$-aryl wherein v is an integer from 1 to 5,

$-(CH_2)_v$-heteroaryl wherein v is as defined above,

$-(CH_2)_v$-cycloalkyl wherein v is as defined above,

$-(CH_2)_p$-X-$(CH_2)_q$-aryl wherein X is O or S and p and q is each zero or an integer of 1 to 5, and the sum of p + q is not greater than an integer of 5,

$-(CH_2)_p$-X-$(CH_2)_q$-heteroaryl wherein X, p, and q are as defined above,

$-(CH_2)_tNR^6R^{6a}$, wherein t is zero or an integer of from 1 to 9 and R^6 and R^{6a} are each the same or different and are as defined above for R^5,

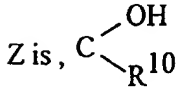
$-(CH_2)_vSR^5$, wherein v and R^5 are as defined above,

$-(CH_2)_vCO_2R^5$, wherein v and R^5 are as defined above, or

$-(CH_2)_vCONR^6R^{6a}$, wherein R^6 and R^{6a} are the same or different and are as defined above for R^5 and v is as defined above;

R^3 is additionally $-(CH_2)_rR^7$ wherein r is an integer from 1 to 5 and R^7 is 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl, or 1,3,-dihydro-1,3-dioxo-benzo[f]isoindol-2-yl;

Y is CH or N;

Z is, 

wherein R^{10} is as defined above for R^2 and R^3, and is independently the same or different from R^2 and R^3 provided that

when Z is $C(OH)R^{10}$, then R^4 must be OH,

C=O,

C=NOR^5 wherein R^5 is as defined above, or

C=N-NR^{6}R^{6a} wherein R^6 and R^{6a} are the same or different and are as defined above for R^5;

W is -CHR^5 wherein R^5 is as defined above;

n is zero or an integer of 1;

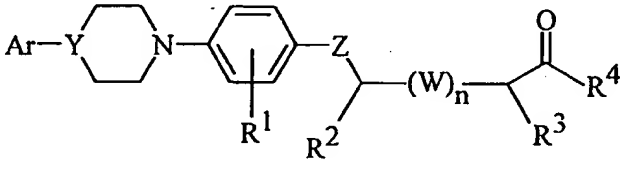
R^4 is OH,

NR^{6}R^{6a} wherein R^6 and R^{6a} are the same or different and are as defined above for R^5, when R^4 is NR^{6}R^{6a} then Z must be C=O or

NHOR^9 wherein R^9 is hydrogen, alkyl, or benzyl;

and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

Especially preferred MMP inhibitors have the formula



Ar is selected from phenyl,

phenyl substituted with

alkyl,

NO_2,

halogen,

OR^5 wherein R^5 is hydrogen or alkyl,

CN,

CO_2R^5 wherein R^5 is as defined above,

SO_3R^5 wherein R^5 is as defined above,

CHO,

COR^5 wherein R^5 is as defined above,

$CONHR^5$ wherein R^5 is as defined above, or

$NHCOR^5$ wherein R^5 is as defined above,

2-naphthyl, or

heteroaryl;

R^1 is selected from hydrogen,

methyl,

ethyl,

NO_2,

halogen,

OR^5 wherein R^5 is as defined above,

CN,

CO_2R^5 wherein R^5 is as defined above,

SO_3R^5 wherein R^5 is as defined above,

CHO, or

COR^5 wherein R^5 is as defined above;

R^2 and R^3 are the same or different and independently selected from hydrogen,

alkyl,

$-(CH_2)_v$-aryl wherein v is an integer from 1 to 5,

$-(CH_2)_v$-heteroaryl wherein v is as defined above,

$-(CH_2)_v$-cycloalkyl wherein v is as defined above,

$-(CH_2)_p$-X-$(CH_2)_q$-aryl wherein X is O or S and p and q is each zero or an integer of 1 to 5, and the sum of p + q is not greater than an integer of 5,

$-(CH_2)_p$-X-$(CH_2)_q$-heteroaryl wherein X, p, and q are as defined above,

$-(CH_2)_tNR^6R^{6a}$, wherein t is zero or an integer of from 1 to 9 and R^6 and R^{6a} are each the same or different and are as defined above for R^5,

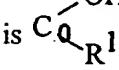
$-(CH_2)_vSR^5$, wherein v and R^5 are as defined above,

$-(CH_2)_vCO_2R^5$, wherein v and R^5 are as defined above, or

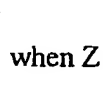
$-(CH_2)_vCONR^6R^{6a}$, wherein R^6 and R^{6a} are the same or different and are as defined above for R^5 and v is as defined above;

R^3 is additionally $-(CH_2)_rR^7$ wherein r is an integer from 1 to 5 and R^7 is 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl, or 1,3,-dihydro-1,3-dioxo-benzo[f]isoindol-2-yl;

Y is CH or N;

Z is  ,

wherein R^{10} is as defined above for R^2 and R^3, and is independently the same or different from R^2 and R^3 provided that

when Z is  , then R^4 must be OH,

C=O,

$C=NOR^5$ wherein R^5 is as defined above, or

$C=N-NR^6R^{6a}$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^5;

W is $-CHR^5$ wherein R^5 is as defined above;

n is zero or an integer of 1;

R^4 is OH,

NR^6R^{6a} wherein R^6 and R^{6a} are the same or different and are as defined above for R^5, when R^4 is NR^6R^{6a} then Z must be C=O or

$NHOR^9$ wherein R^9 is hydrogen, alkyl, or benzyl;

and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

Preferred compounds to be employed include:

4-Oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid;

4-Oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid, potassium salt;

N-Hydroxy-4-oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyramide;

E/Z-4-Hydroxyimino-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid;

E/Z-4-Benzyloxyimino-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid;

4-Oxo-4-[4-(4-phenyl-piperazin-1-yl)-phenyl]-butyric acid; and

(±)3-Methyl-5-oxo-5-[4-(4-phenyl-piperidin-1-yl)-phenyl]-pentanoic acid.

A compound which is 4-oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid.

A compound according to Claim 5 which is selected from the group consisting of:

4-Oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid;

4-Oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid, potassium salt;

N-Hydroxy-4-oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyramide;

E/Z-4-Hydroxyimino-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid;

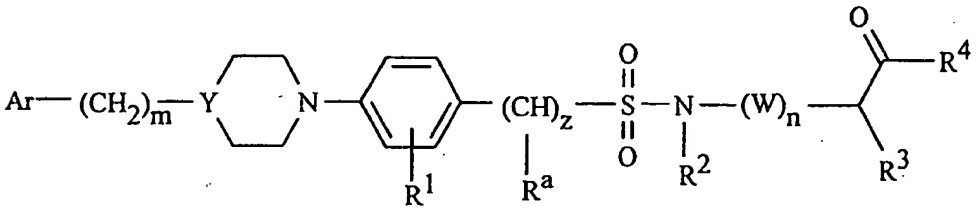
E/Z-4-Benzyloxyimino-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid;

4-Oxo-4-[4-(4-phenyl-piperazin-1-yl)-phenyl]-butyric acid; and

(±)3-Methyl-5-oxo-5-[4-(4-phenyl-piperidin-1-yl)-phenyl]-pentanoic acid.

A compound which is 4-oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid.

Similar compounds which are sulfonamide derivatives have the formula:



wherein:

Ar is selected from phenyl;

phenyl substituted with alkyl, $-NO_2$, halogen, $-OR^5$, -CN, $-CO_2R^5$, $-SO_3R^5$, -CHO, $-COR^5$, $-CONHR^5$, $-NHR^5$, or $-NHCOR^5$;

heteroaryl; or

2-naphthyl;

R^1 is hydrogen, methyl, $-NO_2$, -Cl, $-NH_2$, $-NHCO_2CH_3$, -OH, or $-CO_2H$;

R^2 and R^3 are the same or different and are independently selected from hydrogen, alkyl, $-(CH_2)_v$-aryl, $-(CH_2)_v$-heteroaryl, $-(CH_2)_v$-cycloalkyl, $-(CH_2)_p$-X-$(CH_2)_q$-aryl, $-(CH_2)_p$-X-$(CH_2)_q$-heteroaryl, $-(CH_2)_tNR^6R^{6a}$, $-(CH_2)_vR^7$, $-(CH_2)_vCO_2R^5$, $-(CH_2)_vCONR^6R^{6a}$, or $-(CH_2)_vSR^5$;

m is zero or 1;

Y is CH or N; provided that when m = 1, Y does not = N;

z is zero or 1;

z is zero or 1;

W is $-CHR^8$;

n is zero or 1;

R^4 is -OH, $-NR^6R^{6a}$, or $-NHOR^9$;

R^5 is hydrogen or alkyl;

v is 1 to 5;

X is O or S;

p and q are independently 1 to 5, provided that p+q is not greater than 5;

t is 1 to 9;

R^6 and R^{6a} are each the same or different and are hydrogen or alkyl;

R^7 is 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl, or 1,3-dihydro-1,3-dioxo-benzo[f]isoindol-2-yl;

R^8 is hydrogen or alkyl; and

R^9 is hydrogen, alkyl, or benzyl; or

a pharmaceutically acceptable salt thereof.

Specific sulfonamide derivatives to be employed in the present method include:

[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetic acid;

N-Hydroxy-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetamide;

3-[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(±)-5-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

[4-(4-Phenyl-piperazin-1-yl)-benzene-sulfonylamino]-acetic acid;

{Isobutyl-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonyl]amino}-acetic acid;

(S)-4-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-butyric acid;

(R)-2-[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-3-tritylsulfanyl-propionic acid, sodium salt;

(R)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid, disodium salt, monohydrate;

(S)-2-{4-[-4-(4-Hydroxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(S)-2-{4-[-4-(4-Chloro-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid, hydrochloride;

(R)-3-Mercapto-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid, trifluoracetic acid salt;

(S)-2-[4-(4-Benzyl-piperidin-1-yl)-benzenesulfonylamino]-3-phenyl-propionic acid;

(S)-3-(4-Benzyloxy-phenyl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-(4-Hydroxy-phenyl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperazin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-2-{4-[-4-(3-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(S)-2-{4-[-4-(3-Hydroxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid hydrobromide;

(S)-2-{4-[-4-(4-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(R)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetic acid;

N-Hydroxy-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetamide;

3-[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(±)-5-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

[4-(4-Phenyl-piperazin-1-yl)-benzene-sulfonylamino]-acetic acid;

{Isobutyl-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonyl]amino}-acetic acid;

(S)-4-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-butyric acid;

(R)-2-[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-3-tritylsulfanyl-propionic acid, sodium salt;

(R)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid, disodium salt, monohydrate;

(S)-2-{4-[-4-(4-Hydroxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(S)-2-{4-[-4-(4-Chloro-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid, hydrochloride;

(R)-3-Mercapto-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid, trifluoracetic acid salt;

(S)-2-[4-(4-Benzyl-piperidin-1-yl)-benzenesulfonylamino]-3-phenyl-propionic acid;

(S)-3-(4-Benzyloxy-phenyl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-(4-Hydroxy-phenyl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperazin-1-yl)-benzenesulfonylamino]-propionic acid;

(S)-2-{4-[-4-(3-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(S)-2-{4-[-4-(3-Hydroxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid hydrobromide;

(S)-2-{4-[-4-(4-Methoxy-phenyl)-piperazin-1-yl]-benzenesulfonylamino}-3-phenyl-propionic acid;

(R)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-4-Methyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-pentanoic acid;

(S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid;

(R)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid; and

(S)-3-(1H-Indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid.

Additional specific compounds which can be used include:

2-(Dibenzofuran-2-sulfonylamino)-3-(4-fluoro-phenyl)-propionic acid;

2-(Dibenzofuran-2-sulfonylamino)-3-phenyl-propionic acid;

3-(4-tert-Butoxy-phenyl)-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

(Dibenzofuran-2-sulfonylamino)-phenyl-acetic acid;

3-tert-Butoxy-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

2-(Dibenzofuran-2-sulfonylamino)-3-(1H-imidazol-4-yl)-propionic acid;

2-(Dibenzofuran-2-sulfonylamino)-3-hydroxy-propionic acid;

3-Benzyloxy-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

6-Benzyloxycarbonylamino-2-(dibenzofuran-2-sulfonylamino)-hexanoic acid;

5-Benzyloxycarbonylamino-2-(dibenzofuran-2-sulfonylamino)-pentanoic acid;

(Dibenzofuran-2-sulfonylamino)-(4-methoxy-phenyl)-acetic acid;

3-Chloro-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

3-(4-Benzyloxy-phenyl)-2-(dibenzofuran-2-sulfonylamino)-propionic acid;

2-(Dibenzofuran-2-sulfonylamino)-5-p-tolyl-sulfanylamino-pentanoic acid;

2-(Dibenzofuran-2-sulfonylamino)-4-mercapto-butyric acid;

3-(4-Bromo-phenyl)-2-(dibenzofuran-2-sulfonyl-amino)-propionic acid;

2-(Dibenzofuran-2-sulfonylamino)-butyric acid;

1-(Dibenzofuran-2-sulfonylamino)-cyclopropane-carboxylic acid;

3-(4-Chloro-phenyl)-2-(dibenzofuran-2-sulfonyl-amino)-propionic acid;

2-(Dibenzofuran-2-sulfonylamino)-3-(1H-indol-3-yl)-propionic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(4-fluoro-benzenesulfonylamino)-hexanoic-acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(4-methoxy-benzenesulfonylamino)-hexanoic acid;

6-(4-Bromo-benzenesulfonylamino)-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic-acid;

6-(2-Acetylamino-thiazole-5-sulfonylamino)-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic-acid;

6-(4-Acetylamino-benzenesulfonylamino)-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic-acid;

6-Benzenesulfonylamino-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(pentane-1-sulfonylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(naphthalene-2-sulfonylamino)-hexanoic-acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(naphthalene-1-sulfonylamino)-hexanoic-acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-phenyl-ethenesulfonylamino)-hexanoic-acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-phenyl-acetylamino-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-chloro-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-chloro-phenoxy)-2-methyl-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(pyridin-4-ylsulfanyl)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(2,4-dichloro-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-thiophen-2-yl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(3-phenyl-acryloylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(7-phenyl-heptanoylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(2-trifluoromethyl-phenyl)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-phenoxy-butyrylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-phenyl-sulfanyl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-phenoxy-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(3, 4-dimethoxy-phenyl)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-tert-butyl-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(3, 4-dimethoxy-phenyl)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-cyclopent-1-enyl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-methoxy-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(naphthalen-1-yloxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-nitro-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[4-(4-chloro-3-methyl-phenoxy)-butyrylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-methoxy-phenyl)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-pyridin-3-yl-acetylamino)-hexanoic acid;

6-(2-Benzo[1,3]dioxol-5-yl-acetylamino)-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-pyridin-2-yl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-tert-butyl-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(3,4-dimethoxy-phenyl)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-cyclopent-1-enyl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-methoxy-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(naphthalen-1-yloxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-nitro-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[4-(4-chloro-3-methyl-phenoxy)-butyrylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-methoxy-phenyl)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-pyridin-3-yl-acetylamino)-hexanoic acid;

6-(2-Benzo[1,3]dioxol-5-yl-acetylamino)-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-pyridin-2-yl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[4-(4-nitro-phenyl)-butyrylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-tert-butyl-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(3,4-dimethoxy-phenyl)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-cyclopent-1-enyl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[2-(4-methoxy-phenoxy)-acetylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(4-phenyl-butyrylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[4-(4-chloro-3-methyl-phenoxy)-butyrylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-chloro-phenyl)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-methoxy-phenyl)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-pyridin-3-yl-acetylamino)-hexanoic acid;

6-(2-Benzo[1,3]dioxol-5-yl-acetylamino)-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2-naphthalen-1-yl-acetylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-[3-(4-chloro-phenoxy)-propionylamino]-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(6-phenyl-hexanoylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(4-thiophen-2-yl-butyrylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(2,4,6-triisopropyl-benzoylamino)-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-isobutoxycarbonylamino-hexanoic acid;

2-(4′-Bromo-biphenyl-4-sulfonylamino)-6-(9H-fluoren-9-ylmethoxycarbonylamino)-hexanoic acid;

6-(Adamantan-1-yloxycarbonylamino)-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic acid; and

6-Allyloxycarbonylamino-2-(4′-bromo-biphenyl-4-sulfonylamino)-hexanoic acid.

Numerous succinamide MMP inhibitors are known and can be utilized in the method of this invention. Typical succinamides include:

2S,N^1-Dihydroxy-3R-isobutyl-N^4-{1S-[2-(2-methoxy-ethoxymethoxy)ethylcarbamoyl]-2,2-dimethyl-propyl}-succinamide;

2S-Allyl-N^1-hydroxy-3R-isobutyl-N^4-{1S-[2-(2-methoxy-ethoxymethoxy)ethylcarbamoyl]-2-phenyl-ethyl}-succinamide;

2S-Allyl-N^1-hydroxy-3R-isobutyl-N^4-{1S-[2-(2-methoxy-ethoxymethoxy)ethylcarbamoyl]-2,2-dimethyl-propyl}-succinamide;

2S-Allyl-N^1-hydroxy-3R-isobutyl-N^4-(1S-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethylcarbamoyl]-2,2-dimethyl-propyl}-succinamide;

2S-Allyl-N^4-{1S-[2,2-di-(methoxymethyl)-propylcarbamoyl}-2,2-dimethyl-propyl]-N^1-hydroxy-3R-isobutyl-succinamide;

2S-Allyl-N^4-{1S-[2,2-di-(methoxymethyl)-butylcarbamoyl]-2,2-dimethyl-propyl}-N^1-hydroxy-3R-isobutyl-succinamide;

N^4-Hydroxy-2R-isobutyl-N^1-{1S-[2-(2-methoxy-ethoxy)-ethylcarbamoyl]-2,2-dimethyl-propyl}-3S-(thiophen-2-yl-sulfanylmethyl)-succinamide;

N^4-Hydroxy-2R-isobutyl-N^1-(1S-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethylcarbamoyl}-2,2-dimethyl-propyl)-3S-(thiophen-2-yl-sulfanylmethyl)-succinamide;

N^1-{1S-[2,2-Di-(methoxymethyl)-propylcarbamoyl]-2,2-dimethyl-propyl}-N^4-hydroxy-3R-isobutyl-3S-(thiophen-2-yl-sulfanylmethyl)-succinamide;

N^4-Hydroxy-2R-isobutyl-N^1-{1S-[2-(2-methoxy-ethoxy)-ethylcarbamoyl]-2,2-dimethyl-propyl}-3S-propyl-succinamide;

N^4-(1S-Cyclobutylcarbamoyl-2,2-dimethyl-propyl)-2S,N^1-dihydroxy-3R-isobutyl-succinamide;

N^4-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-2S,N^1-dihydroxy-3R-isobutyl-succinamide;

N^4-(1S-Cyclopentylcarbamoyl-2,2-dimethyl-propyl)-2S,N^1-dihydroxy-3R-isobutyl-succinamide;

N^4-(1S-Cyclohexylcarbamoyl-2,2-dimethyl-propyl)-2S,N^1-dihydroxy-3R-isobutyl-succinamide;

N^4-(1S-Cycloheptylcarbamoyl-2,2-dimethyl-propyl)-2S,N^1-dihydroxy-3R-isobutyl-succinamide;

N^4-(1S-Cyclopropylcarbamoyl-2-mercapto-2-methyl-propyl)-2S,N^1-dihydroxy-3R-isobutyl-succinamide;

N^4-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-2S,N^1-dihydroxy-3R-(3-phenyl-propenyl)-succinamide;

N^4-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-2S,N^1-dihydroxy-3R-(3-phenyl-propyl)-succinamide;

N^4-[2,2-Dimethyl-1S-(2-phenyl-cyclopropylcarbamoyl)-propyl]-2S,N^1-dihydroxy-3R-isobutyl-succinamide;

2S-Allyl-N^4-(1-cyclopropylcarbamoyl-2,2-dimethyl-propyl)-N^1-hydroxy-3R-isobutyl-succinamide;

2S-Allyl-N^4-(1S-cyclopropylcarbamoyl-2-mercapto-2-methyl-propyl)-N^1-hydroxy-3R-isobutyl-succinamide;

N^4-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-N^1-hydroxy-3R-isobutyl-2S-(thiophen-2-ylsulfanylmethyl)-succinamide;

N^4-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-N^1-hydroxy-2S-(4-hydroxy-phenylsulfanylmethyl)-3R-isobutyl-succinamide; and

N^4-(1S-Cyclopropylcarbamoyl-2,2-dimethyl-propyl)-2S-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-N^1-hydroxy-3R-isobutyl-succinamide.

All that is required to practice the present invention is to administer to a mammal suffering from a neurological disorder or suspected of developing a neurological disorder or a wound an effective amount of a matrix metalloprotainase inhibitor. Compounds which can inhibit the actions of matrix metalloproteinase enzymes can be identified utilizing routine in vitro and in vivo assays. Several compounds from within the foregoing classes have been evaluated in such standard assays and determined to be potent matrix metalloproteinase inhibitors. The assays measure the amount by which a test compound reduces the hydrolysis of a thiopeptolide substrate caused by a matrix metalloproteinase enzyme. Such assays are described in detail by Ye, et al., in Biochemistry, Vol. 31, No 45, 1992, (11231-11235), which is incorporated herein by reference.

Thiopeptolide substrates show virtually no decomposition or hydrolysis in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-O Et. A 100 µL assay mixture will contain 50 mM of 2-morpholinoethane sulfonic acid monohydrate (MES, pH 6.0) 10 mM $CaCl_2$, 100 µM thiopeptolide

substrate, and 1 mM 5,5'-dithio-bis-(2-nitro-benzoic acid (DTNB). The thiopeptolide substrate concentration is varied from 10 to 800 μM to obtain Km and Kcat values. The change in absorbance at 405 nm is monitored on a Thermo Max microplate reader (moleucular Devices, Menlo Park, CA) at room temperature (22°C). The calculation of the amount of hydrolysis of the thiopeptolide substrate is based on $E_{412} = 13600\ m^{-1}\ cm^{-1}$ for the DTNB-derived product 3-carboxy-4-nitrothiophenoxide. Assays are carried out with and without matrix metalloproteinase inhibitor compounds, and the amount of hydrolysis is compared for a determination of inhibitory activity of the test compounds.

Several representative compounds have been evaluated for their ability to inhibit various matrix metalloproteinase enzymes. Table 3 below presents inhibitory activity for compounds from various classes. In the table, MMP-1 refers to interstitial collagenase; MMP-2 refers to Gelatinase A; MMP-3 refers to stromelysin; MMP-7 refers to matrilysin; and MMP-9 refers to Gelatinase B. Test compounds were evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of the hydrolytic activity of the respective enzyme.

TABLE 3 (IC_{50} μM)

	MMP1	MMP2	MMP3	MMP7	MMP9
Batimastat is N^4-Hydroxy-N^1-[2-(methylamine)-2-oxo-1-(phenylmethyl)ethyl]-2-(2-methylpropyl)-3-[(2-thienylthio)methyl]-butanediamide	0.005	0.004	0.02		
CDP-845 (Celltech)	0.303	0.0015	0.01		
CGS 27023A (Ciba-Giegy)	0.033	0.01	0.01		0.008
Galardin is N^4-Hydroxy-N^1-[2-(methylamine)-2-oxo-1-(3-indolylmethyl)ethyl]-2-(2-methylpropyl)-butanediamide	0.0004	0.0005	27		0.0002
U24522 (Merck)		0.05	0.02		
RO-31-9790 (Roche)	0.0055	0.006	0.47		
4-Oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyric acid		1.3	0.14		
N-Hydroxy-4-oxo-4-[4-(4-phenyl-piperidin-1-yl)-phenyl]-butyramide		0.04	0.02		
4-Oxo-4-[4-(4-phenyl-piperazin-1-yl)-phenyl]-butyric acid		1.6	0.25		
[4-(4-Phenyl-piperidin-1-yl)-benzenesulfonylamino]-acetic acid		0.21	0.02		
N-Hydroxy-2-[4-(4-phenyl-piperidin-1-yl)-benzene-sulfonylamino]-acetamide		0.81	0.019		
(S)-3-Phenyl-2-[4-(4-phenyl-piperidin-1-yl)-benzene-sulfonylamino]-propionic acid		0.22	0.014		
(S)-2-[4-(4-Benzyl-piperidin-1-yl)-benzenesulfonylamino]-3-phenyl-propionic acid		0.088	0.021		
(S)-2-{4-[-4-(4-Methoxy-phenyl)-piperazin-1-yl]-benzene-sulfonylamino}-3-phenyl-propionic acid		0.033	0.014		
(S)-2-(4′-Bromo-biphenyl-4-sulfonylamino)-3-methyl-butyric acid	3.24	0.025	0.012		
(S)-3-Methyl-2-(4′-nitro-biphenyl-4-sulfonylamino)-butyric acid;		0.013	0.10		

TABLE 3 (IC_{50} μM) (cont'd)

	MMP1	MMP2	MMP3	MMP7	MMP9
(S)-2-(4'-Amino-biphenyl-4-sulfonylamino)-3-methyl-butyric acid		0.044	0.067		
(S)-2-(4'-Bromo-biphenyl-4-sulfonylamino)-3-phenyl-propionic acid		0.026	0.026		
4-(4'-Chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid		0.39	0.12		
4-(4'-Bromo-biphenyl-4-yl)-4-hydroxyimino-butyric acid		0.058	0.11		
4-(4'-Chloro-biphenyl-4-yl)-4-(dimethylhydrazono)-butyric acid		0.73	0.93		
(±)-4-(4'-Chloro-biphenyl-4-yl)-4-hydroxy-butyric acid		0.15	0.28		
(S)-2-(Dibenzofuran-2-sulfonylamino)-4-phenyl-butyric acid		0.265	0.46		
(L)-2-(Dibenzofuran-2-sulfonylamino)-4-methyl-pentanoic acid		0.32	1.18		
(L)-2-(Dibenzofuran-2-sulfonylamino)-3-phenyl-propionic acid		0.89	0.72		
(L)-2-(Dibenzofuran-2-sulfonylamino)-3-methyl-butyric acid		0.084	0.23		
(L)-2-(Dibenzofuran-2-sulfonylamino)-3-tritylsulfanyl-propionic acid		9.4	14.4		
(L)-2-(Dibenzofuran-2-sulfonylamino)-3-mercapto-propionic acid		4.45	0.69		
(S)-4-Dibenzofuran-2-yl-4-oxo-2-(2,2,2-trifluoroacetylamino)-butyric acid		0.72	1.33		
(S)-2-Amino-4-dibenzofuran-2-yl-4-oxo-butyric acid		3.8	33.0		
(S)-2-Acetylamino-4-dibenzofuran-2-yl-4-oxo-butyric acid		0.16	1.55		
(S)-4-Dibenzofuran-2-yl-4-oxo-2-phenylacetylamino-butyric acid		0.084	0.33		
(S)-4-Dibenzofuran-2-yl-4-oxo-2-(3-phenyl-propionylamino)-butyric acid		0.096	0.28		

The compounds to be employed in the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms for treating and preventing heart failure. The compounds can be administered by injection, that is, intra-venously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds can be administered by inhalation, for example, intranasally. Additionally, the compounds can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound as a free base, acid, or a corresponding pharmaceutically acceptable salt of such compound. The active compound generally is present in a concentration of about 5% to about 95% by weight of the formulation.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are

included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit-dose preparation may be varied or adjusted from 1 to 1000 mg, preferably 10 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for the treatment of heart failure, the compounds utilized in the pharmaceutical method of this invention are administered at a dose that is effective to inhibit the hydrolytic activity of one or more matrix metalloproteinase enzymes. The compounds can also be used prophalactically at the same dose levels. The initial dosage of about 1 mg to about 100 mg per kilogram daily will be effective to prevent and treat heart failure. A daily dose range of about 25 to about 75 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. Typical dosages will be from about 0.1 to about 500 mg/kg, and ideally about 2 to about 25 mg/kg.

The following examples illustrate typical formulations that can be utilized in the invention.

Tablet Formulation

Ingredient	Amount (mg)
2-(4'-bromobiphenyl-4-sulfonylamino)-3-methyl-butyric acid	25
Lactose	50
Corn starch (for mix)	10
Corn starch (paste)	10
Magnesium stearate (1%)	5
Total	100

The biphenylsulfonamide, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of atherosclerosis and arthritis.

Preparation for Oral Solution

Ingredient	Amount
(R)-2-(4'-Cyanobiphenyl-4-sulfonylamino)-3-phenyl-propionic acid sodium salt	400 mg
Sorbitol solution (70% N.F.)	40 mL
Sodium benzoate	20 mg
Saccharin	5 mg
Red dye	10 mg
Cherry flavor	20 mg
Distilled water q.s.	100 mL

The sorbitol solution is added to 40 mL of distilled water, and the biphenylsulfonamide is dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 4 mg of invention compound.

Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection is suspended 20 g of (S)-2-(4′-amino-biphenyl-4-sulfonylamino)-3-(3-ethoxyphenyl)-propionic acid. After suspension is complete, the pH is adjusted to 6.5 with 1 N sodium hydroxide, and the volume is made up to 1000 mL with water for injection. The formulation is sterilized, filled into 5.0 mL ampoules each containing 2.0 mL, and sealed under nitrogen.

CLAIMS

What is claimed is:

1. A method for treating and preventing a neurological disorder in a mammal comprising administering an effective amount of a matrix metalloproteinase inhibitor.

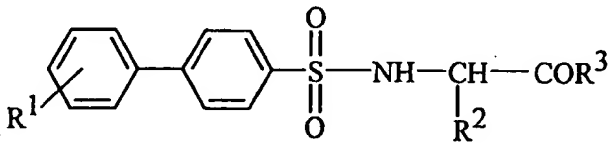
2. The method of Claim 1 wherein the neurological disorder is Alzheimer's disease.

3. The method of Claim 1 wherein the neurological disorder is Huntington's disease.

4. The method of Claim 1 wherein the neurological disorder is Parkinson's disease.

5. The method of Claim 1 wherein the neurological disorder is amyotrophic lateral sclerosis.

6. The method of Claim 1 wherein the MMP inhibitor utilized is a compound of the formula



wherein:

R^1 is C_1-C_6 alkyl, halo, nitro, NR^4R^5, cyano, OR^4, and $COOR^4$;

R^2 is C_1-C_6 alkyl, optionally substituted by phenyl, substituted phenyl, NR^4R^5, OR^6,

carboxy, carboxamido, $H_2N-\overset{\overset{NH}{\|}}{C}-NH-$, thio, methylthio, indole, imidazole, phthalimido, phenyl, and substituted phenyl;

R^3 is OH, OC_1-C_6 alkyl, or NHOH;

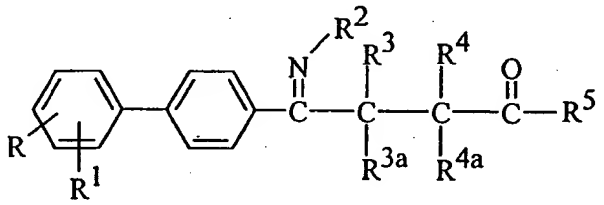
R^4 is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkanoyl;

R^5 is hydrogen or C_1-C_6 alkyl; and

R^6 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl, or substituted phenyl.

7. The method of Claim 6 employing 2-(4′-bromobiphenyl-4-sulfonylamino)-3-methyl-butyric acid.

8. The method of Claim 1 wherein the MMP inhibitor utilized is a compound of the formula



wherein R and R^1 are the same or different and are

hydrogen,

alkyl,

halogen,

nitro,

cyano,

trifluoromethyl,

$-OR^6$ wherein R^6 is hydrogen,

alkyl,

aryl,

arylalkyl,

heteroaryl, or

cycloalkyl,

$-N(R^{6a})-R^6$ wherein R^6 and R^{6a} are the same or different and are

as defined above for R^6, $-O-C(=O)-R^6$ wherein R^6 is as defined above,

$-NH-C(=O)-R^6$ wherein R^6 is as defined above,

$-S-C(=O)-R^6$ wherein R^6 is as defined above,

$-SR^6$ wherein R^6 is as defined above,

$-C(=O)-R^6$ wherein R^6 is as defined above,

$-CH_2-OR^6$ wherein R^6 is as defined above,

$-CH_2-N(R^{6a})-R^6$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-C(=O)-N(R^{6a})-R^6$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-S(=O)-R^6$ wherein R^6 is as defined above,

$-S(=O)_2-R^6$

cycloalkyl, or

heteroaryl, with the proviso that R and R^1 are not both hydrogen;

R^2 is $-OR^6$ wherein R^6 is as defined above, or

$-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6;

R^3, R^{3a}, R^4, and R^{4a} are the same or different and are

hydrogen,

fluorine,

alkyl,

$-(CH_2)_n$-aryl wherein n is an integer from 1 to 6,

$-(CH_2)_n$-heteroaryl wherein n is as defined above,

$-(CH_2)_n$-cycloalkyl wherein n is as defined above,

$-(CH_2)_p$-X-$(CH_2)_q$-aryl wherein X is O, S, SO, SO_2, or NH, and p and q are each zero or an integer of 1 to 6, and the sum of p + q is not greater than six,

$-(CH_2)_p$-X-$(CH_2)_q$-heteroaryl wherein X, p, and q are as defined above, or

$-(CH_2)_n-R^7$ wherein R^7 is

N-phthalimido,

N-2,3-naphthyimido,

$-OR^6$ wherein R^6 is as defined above,

$-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-SR^6$ where R^6 is as defined above,

$-S(=O)-R^6$ wherein R^6 is as defined above,


-S-R^6 wherein R^6 is as defined above,


-O-C-R^6 wherein R^6 is as defined above,


-N-C-R^6 wherein R^6 and R^{6a} are the same

R^{6a}

or different and are as defined above for R^6,


-S-C-R^6 wherein R^6 is as defined above,


-C-R^6 wherein R^6 is as defined above,


-C-OR^6 wherein R^6 is as defined above, or


-C-N-R^6 wherein R^6 and R^{6a} are the same

R^{6a}

or different and are as defined above for R^6, and

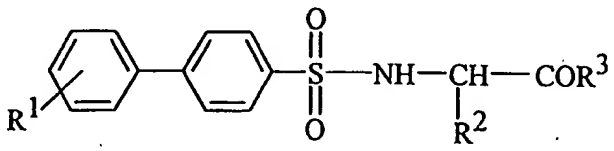
n is as defined above;

R^5 is OH or SH; with the proviso that R^3, R^{3a}, R^4, and R^{4a} are hydrogen or at least one of R^3, R^{3a}, R^4, or R^{4a} is fluorine; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

9. The method of Claim 8 wherein the MMP inhibitor employed is 4-(4′-chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid.

10. A method of promoting wound healing in a mammel comprising administering an effective amount of a matrix metalloproteinase inhibitor.

11. The method of Claim 10 wherein the MMP inhibitor utilized is a compound of the formula



wherein:

R^1 is C_1-C_6 alkyl, halo, nitro, NR^4R^5, cyano, OR^4, and $COOR^4$;

R^2 is C_1-C_6 alkyl, optionally substituted by phenyl, substituted phenyl, NR^4R^5, OR^6,

carboxy, carboxamido, H_2N-C-NH-, thio, methylthio, indole, imidazole, phthalimido, phenyl, and substituted phenyl;

R^3 is OH, OC_1-C_6 alkyl, or NHOH;

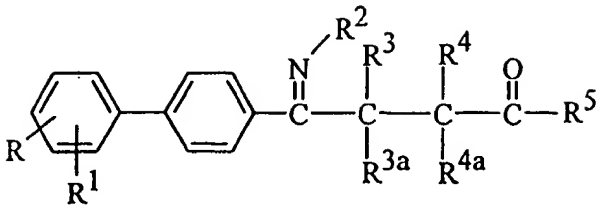
R^4 is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkanoyl;

R^5 is hydrogen or C_1-C_6 alkyl; and

R^6 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl, or substituted phenyl.

12. The method of Claim 11 wherein the MMP inhibitor utilized is 2-(4'-bromobiphenyl-4-sulfonylamino)-3-methyl-butyric acid.

13. The method of Claim 10 wherein the MMP inhibitor utilized is a compound of the formula



wherein R and R^1 are the same or different and are

hydrogen,

alkyl,

halogen,

nitro,

cyano,

trifluoromethyl,

$-OR^6$ wherein R^6 is hydrogen,

alkyl,

aryl,

arylalkyl,

heteroaryl, or

cycloalkyl,

$-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are

as defined above for R^6, $-O-C(=O)-R^6$ wherein R^6 is as defined above,

$-NH-C(=O)-R^6$ wherein R^6 is as defined above,

$-S-C(=O)-R^6$ wherein R^6 is as defined above,

$-SR^6$ wherein R^6 is as defined above,

$-C(=O)-R^6$ wherein R^6 is as defined above,

$-CH_2-OR^6$ wherein R^6 is as defined above,

$-CH_2-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-C(=O)-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-S(=O)_2-R^6$ wherein R^6 is as defined above,

cycloalkyl, or

heteroaryl, with the proviso that R and R^1 are not both hydrogen;

R^2 is $-OR^6$ wherein R^6 is as defined above, or

$-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6;

R^3, R^{3a}, R^4, and R^{4a} are the same or different and are

hydrogen,

fluorine,

alkyl,

$-(CH_2)_n$-aryl wherein n is an integer from 1 to 6,

$-(CH_2)_n$-heteroaryl wherein n is as defined above,

$-(CH_2)_n$-cycloalkyl wherein n is as defined above,

$-(CH_2)_p-X-(CH_2)_q$-aryl wherein X is O, S, SO, SO_2, or NH, and p and q are each zero or an integer of 1 to 6, and the sum of p + q is not greater than six,

$-(CH_2)_p-X-(CH_2)_q$-heteroaryl wherein X, p, and q are as defined above, or

$-(CH_2)_n-R^7$ wherein R^7 is

N-phthalimido,

N-2,3-naphthyimido,

$-OR^6$ wherein R^6 is as defined above,

$-N(R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-SR^6$ where R^6 is as defined above,

$-S(=O)-R^6$ wherein R^6 is as defined above,

$-S(=O)_2-R^6$ wherein R^6 is as defined above,

$-O-C(=O)-R^6$ wherein R^6 is as defined above,

$-N(C(=O)-R^6)(R^{6a})$ wherein R^6 and R^{6a} are the same or different and are as defined above for R^6,

$-S-C(=O)-R^6$ wherein R^6 is as defined above,

$-C(=O)-R^6$ wherein R^6 is as defined above,


-C-OR^6 wherein R^6 is as defined above, or


-C-N-R^6 wherein R^6 and R^{6a} are the same

R^{6a}

or different and are as defined above for R^6, and

n is as defined above;

R^5 is OH or SH; with the proviso that R^3, R^{3a}, R^4, and R^{4a} are hydrogen or at least one of R^3, R^{3a}, R^4, or R^{4a} is fluorine; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

14. The method of Claim 13 employing 4-(4′-chloro-biphenyl-4-yl)-4-hydroxyimino-butyric acid.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 97/21532

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/18 A61K31/445 A61K31/495 C07K5/06 C07K5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 44315 A (WARNER-LAMBERT COMPANY) 27 November 1997 see claims 1-18 see page 21, line 16 - page 22, line 2 ---	10-12
P,X	WO 97 19068 A (WARNER-LAMBERT COMPANY) 29 May 1997 see claims 1,13-15,20-22,26 ---	10
P,X	WO 97 23459 A (WARNER-LAMBERT COMPANY) 3 July 1997 see claims 1,19-21,27-30,35,36 ---	10
X	WO 96 11209 A (CHIROSCIENCE LIMITED) 18 April 1996 cited in the application see claims 1-14,17-19,21-23 --- -/--	1,2,10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 1998	24.04.98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Siatou, E

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INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 97/21532

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 07695 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA....) 23 March 1995 see claims 1-13 see page 4, line 3 - line 11 see page 12, line 25 - line 33	1,2,10
X	EP 0 606 046 A (CIBA-GEIGY AG) 13 July 1994 see claims 1-24 see page 8, line 38 - line 50 & US 5 455 258 A cited in the application	1,2,10
X	WO 96 15096 A (BAYER CORPORATION) 23 May 1996 cited in the application see claims 1,7-12,17,18	1,10
X	WO 96 38434 A (WARNER-LAMBERT COMPANY) 5 December 1996 see claims 1,18-20,26,31,32	10
A	US 3 784 701 A (A. S. TOMCUFCIK ET AL) 8 January 1974 cited in the application see claims 1-3	1-14
A	BEELEY N R A ET AL: "INHIBITORS OF MATRIX METALLOPROTEINASES (MMP S)" CURRENT OPINION IN THERAPEUTIC PATENTS, vol. 4, no. 1, January 1994, pages 7-16, XP002043031 see page 9, left-hand column, line 3 - line 12 see page 9, left-hand column, line 18 - line 28 see page 9, right-hand column, line 1 - page 14, right-hand column	1-14
A	BECKETT R P ET AL: "RECENT ADVANCES IN MATRIX METALLOPROTEINASE INHIBITOR RESEARCH" DRUG DISCOVERY TODAY, vol. 1, no. 1, January 1996, pages 16-26, XP002043033 see figures 1-3 see page 25, right-hand column, last paragraph	1-14

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1

INTERNATIONAL SEARCH REPORT

Interna[illegible]al Application No
PCT/US 97/21532

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MORPHY J R ET AL: "MATRIX METALLOPROTEINASE INHIBITORS: CURRENT STATUS" CURRENT MEDICINAL CHEMISTRY, vol. 2, 1995, pages 743-762, XP002043028 -----	1-14

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/21532

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/21532

FURTHER INF RMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1-14

because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Remark : Although claims 1-14
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: ial Application No
PCT/US 97/21532

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